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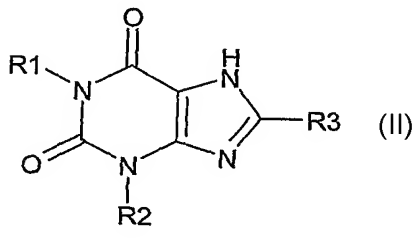
(54) Title: NOVEL COMPOUNDS



(II)

(57) Abstract: The present invention provides therapeutically active compounds which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, having the formula (II): wherein R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3, R^2 is selected from: C_{2-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl, and R^3 is selected from halogen and CN.

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NOVEL COMPOUNDS

The present invention relates to therapeutically active compounds which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial.

Dyslipidaemia is a general term used to describe individuals with aberrant lipoprotein profiles. Clinically, the main classes of compounds used for the treatment of patients with dyslipidaemia, and therefore at risk of cardiovascular disease are the statins, fibrates, bile-acid binding resins and nicotinic acid. Nicotinic acid (Niacin, a B vitamin) has been used clinically for over 40 years in patients with various forms of dyslipidaemia. The primary mode of action of nicotinic acid is via inhibition of hormone-sensitive triglyceride lipase (HSL), which results in a lowering of plasma non-esterified fatty acids (NEFA) which in turn alters hepatic fat metabolism to reduce the output of LDL and VLDL (low and very low density lipoprotein). Reduced VLDL levels are thought to lower cholesterol ester transfer protein (CETP) activity to result in increased HDL (high density lipoprotein) levels which may be the cause of the observed cardiovascular benefits. Thus, nicotinic acid produces a very desirable alteration in lipoprotein profiles; reducing levels of VLDL and LDL whilst increasing HDL. Nicotinic acid has also been demonstrated to have disease modifying benefits, reducing the progression and increasing the regression of atherosclerotic lesions and reducing the number of cardiovascular events in several trials.

The observed inhibition of HSL by nicotinic acid treatment is mediated by a decrease in cellular cyclic adenosine monophosphate (cAMP) caused by the G-protein-mediated inhibition of adenylyl cyclase. Recently, the G-protein coupled receptors HM74 and HM74A have been identified as receptors for nicotinic acid (PCT patent application WO02/84298; Wise et. al. J Biol Chem., 2003, 278 (11), 9869-9874). The DNA sequence of human HM74A may be found in Genbank; accession number AY148884. Two further papers support this discovery, (Tunaru et. al. Nature Medicine, 2003, 9(3), 352-255 and Soga et. al. Biochem Biophys Res Commun., 2003, 303 (1) 364-369), however the nomenclature differs slightly. In the Tunaru paper what they term human HM74 is in fact HM74A and in the Soga paper HM74b is identical to HM74A. Cells transfected to express HM74A and/or HM74 gain the ability to elicit G_i G-protein mediated responses following exposure to nicotinic acid. In mice lacking the homologue of HM74A (m-PUMA-G) nicotinic acid fails to reduce plasma NEFA levels.

Certain xanthine derivatives have been synthesised and disclosed in the prior art. For example, EP0389282 discloses xanthine derivatives as potential mediators of cerebrovascular disorders. A range of xanthine derivatives were identified as adenosine receptor antagonists by Jacobson et. al. in J. Med. Chem., 1993, 36, 2639-2644.

We now present a group of xanthine derivatives which are selective agonists of the nicotinic acid receptor HM74A and are thus of benefit in the treatment, prophylaxis and suppression of diseases where under-activation of this receptor either contributes to the disease or where activation of the receptor will be beneficial.

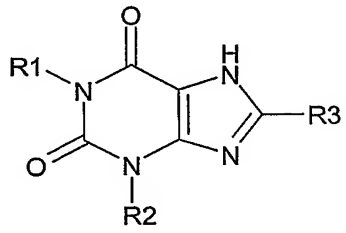
Summary of the Invention

The present invention provides therapeutically active xanthine derivatives and the use of these derivatives in therapy, particularly in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, in particular diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. The compounds may also be of use in the treatment of inflammatory diseases or conditions, as set out further below.

Intermediates, formulations, methods and processes described herein form further aspects of the invention.

Detailed Description of the Invention

According to one aspect of this invention, we provide a compound of Formula (I)



(I)

and a physiologically functional derivative thereof, wherein

R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3;

R^2 is selected from: C_{3-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl;
and R^3 is selected from halogen and CN;
with the proviso that:
(i) when R^3 represents Cl, and R^1 represents ethyl, R^2 is other than propyl;
(ii) when R^3 represents Br, and R^1 represents propyl, R^2 is other than propyl;
(iii) when R^3 represents Cl or Br, and R^1 represents butyl, R^2 is other than butyl; and
(iv) when R^1 represents C_{1-4} alkyl, CH_2CN, or $(CH_2)_3CF_3$, R^2 is other than branched alkyl.

The compounds are of use in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, in particular diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, as well as the cardiovascular indications associated with type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such the compounds of the present invention may find use as agonists or partial agonists of HM74A (HM74A modulators).

In particular embodiments, R^1 is selected from: hydrogen, C_{1-4} alkyl, CH_2CN and $(CH_2)_3CF_3$; In more particular embodiments R^1 is selected from: hydrogen and methyl.

In certain embodiments, R^2 is selected from: C_{3-10} unsubstituted alkyl, C_{1-6}alkyl with one or more CN substitutions, C_{1-10} alkyl with one or more fluorine substitutions, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl. Particularly R^2 is selected from: C_{3-10} unsubstituted alkyl; $(CH_2)_{1-5}CN$; C_{2-5} alkyl with one or more fluorine substitutions; C_5 alkenyl; and C_{1-4} alkyl substituted with cycloalkyl. More particularly R^2 is selected from C_{4-6} unsubstituted n-alkyl, for example pentyl; $(CH_2)_{1-3}CN$, for example, $(CH_2)CN$ or $(CH_2)_3CN$; C_{3-4} alkyl with one or more fluorine substitutions, in particular where the terminal carbon is fully saturated with fluorine, for example $(CH_2)_{2-3}CF_3$; and C_5 alkenyl, in particular, where there is only one double bond, for example where the double bond is located between the fourth and fifth carbons (terminal alkenyl).

In particular embodiments, R^3 represents halogen. More particularly, R^3 is selected from: chlorine and bromine. Most particularly, R^3 represents chlorine.

It is to be understood that the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described hereinabove.

Particular compounds of the present invention include:

(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)acetonitrile,
3-Butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Bromo-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-1-propyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
3-Butyl-8-chloro-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione,
(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile,
8-Chloro-3-(2-cyclopropylethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
4-(8-Chloro-1-methyl-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile,
8-Chloro-1-ethyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
1-Methyl-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile,
8-Chloro-3-propyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3-methylbutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione,
3-Butyl-1-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile,
8-Chloro-3-(4-penten-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-hexyl-3,7-dihydro-1*H*-purine-2,6-dione,
4-(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile,
8-Chloro-3-hexyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione,
3-Butyl-8-chloro-1-ethyl-3,7-dihydro-1*H*-purine-2,6-dione,
[8-Chloro-3-(2-cyclopropylethyl)-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl]acetonitrile,
(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile,
8-Chloro-1-(4,4,4-trifluorobutyl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
2,2'-(8-Chloro-2,6-dioxo-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl)diacetonitrile,
8-Chloro-1-methyl-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(2-cyclohexylethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
1,3-Dibutyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile,
1,3-Dibutyl-8-iodo-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(4-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(6-methylheptyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-octyl-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-decyl-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclohexylmethyl)-3,7-dihydro-1H-purine-2,6-dione,
(+/-)-8-Chloro-3-(3-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(2-cyclopentylethyl)-3,7-dihydro-1H-purine-2,6-dione,

8-Chloro-3-(cyclopropylmethyl)-3,7-dihydro-1H-purine-2,6-dione,
(+/-)-8-Chloro-3-(2-methylbutyl)-3,7-dihydro-1H-purine-2,6-dione,
(+/-)-8-Chloro-3-(2-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclobutylmethyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclopentylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3-cyclopropylpropyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(2-cyclobutylethyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(4-fluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3-fluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(5-fluoropentyl)-3,7-dihydro-1*H*-purine-2,6-dione,
4-(8-Chloro-1-methyl-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile,
3-(3-Buten-1-yl)-8-chloro-3,7-dihydro-1H-purine-2,6-dione,
6-(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)-2,2-dimethylhexanenitrile,
8-Chloro-3-(6-fluorohexyl)-3,7-dihydro-1H-purine-2,6-dione.

Throughout the present specification and the accompanying claims the words "comprise" and "include" and variations such as "comprises", "comprising", "includes" and "including" are to be interpreted inclusively. That is, these words are intended to convey the possible inclusion of other elements or integers not specifically recited, where the context allows.

As used herein, the terms "halogen" or "halo" refer to fluorine, chlorine, bromine and iodine.

As used herein, the term "alkyl" (when used as a group or as part of a group) refers to a straight or branched hydrocarbon chain unless specified otherwise, containing the specified number of carbon atoms. For example, C_3-C_{10}alkyl means a straight or branched hydrocarbon chain containing at least 3 and at most 10 carbon atoms. Examples of alkyl as used herein include, but are not limited to methyl (Me), ethyl (Et), n-propyl and i-propyl. The term "n-alkyl" refers specifically to an un-branched hydrocarbon chain.

As used herein, the term "cycloalkyl" refers to a hydrocarbon ring containing between 3 and 6 carbon atoms, comprising no heteroatoms or conjugated double bonds. Examples of cycloalkyl as used herein include, but are not limited to cyclopropyl and cyclohexyl.

As used herein, the term "alkenyl" refers to a straight or branched hydrocarbon chain containing the specified number of carbon atoms which contains one or more double bonds.

As used herein, where a group is referred to as being "substituted" with another group or having "one or more substitutions" unless a particular position for such a substitution is specified it is to be understood that a substitution may be present at any position in the group.

As used herein, the term "physiologically functional derivative" refers to any pharmaceutically acceptable derivative of a compound of the present invention, for example an amide thereof, and includes any pharmaceutically acceptable salt of a compound of formula (I), and any pharmaceutically acceptable solvate of a compound of formula (I) which, upon administration to a mammal, such as a human, is capable of providing (directly or indirectly) a compound of formula (I) or an active metabolite or residue thereof. It will be appreciated by those skilled in the art that the compounds of formula (I) may be modified to provide physiologically functional derivatives thereof at any of the functional groups in the compounds, and that the compounds of formula (I) may be so modified at more than one position.

As used herein, the term "pharmaceutically acceptable" used in relation to an ingredient (active ingredient or excipient) which may be included in a pharmaceutical formulation for administration to a patient, refers to that ingredient being acceptable in the sense of being compatible with any other ingredients present in the pharmaceutical formulation and not being deleterious to the recipient thereof.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I), a salt thereof or a physiologically functional derivative thereof) and a solvent. Such solvents for the purposes of the present invention may not interfere with the biological activity of the solute. The solvent used may be a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. An example of a solvent that may be used is water, in which case the solvate may be referred to as a hydrate of the solute in question.

It will be appreciated that, for pharmaceutical use, the "salt or solvate" referred to above will be a pharmaceutically acceptable salt or solvate. However, other salts or solvates may find use, for example, in the preparation of a compound of formula (I) or in the preparation of a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutically acceptable salts include those described by Berge, Bighley and Monkhouse, *J. Pharm. Sci.*, 1977, 66, 1-19. Suitable pharmaceutically acceptable salts include alkali metal salts formed from the addition of alkali metal bases such as alkali metal hydroxides. Examples of suitable alkali metal salts are sodium salt or potassium salt. Other suitable pharmaceutically acceptable salts include alkaline earth metal salts such as calcium salt or magnesium salt, ammonium salts; or salts with organic bases such as ethanolamine, triethanolamine, ethylene diamine, triethylmine, choline and meglumine; or salts with amino acids such as arginine, lysine and histidine.

Compounds of formula (I) are of potential therapeutic benefit in the treatment and amelioration of the symptoms of many diseases of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis,

arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds may also find favour as therapeutics for coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

Furthermore, it is also believed that the HM74 and HM74A receptors are involved in inflammation. Inflammation represents a group of vascular, cellular and neurological responses to trauma. Inflammation can be characterised as the movement of inflammatory cells such as monocytes, neutrophils and granulocytes into the tissues. This is usually associated with reduced endothelial barrier function and oedema into the tissues. Inflammation with regards to disease typically is referred to as chronic inflammation and can last up to a lifetime. Such chronic inflammation may manifest itself through disease symptoms. The aim of anti-inflammatory therapy is therefore to reduce this chronic inflammation and allow for the physiological process of healing and tissue repair to progress.

Examples of inflammatory diseases or conditions for which the compounds of the present invention may demonstrate utility include those of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In particular, the compounds of this invention are useful in the treatment and prevention of inflammation, diabetes and cardiovascular diseases or conditions including atherosclerosis, arteriosclerosis, hypertriglyceridemia, and mixed dyslipidaemia.

Nicotinic acid has a significant side effect profile, possibly because it is dosed at high level (gram quantities daily). The most common side effect is an intense cutaneous flushing. In certain embodiments of the present invention the compounds may exhibit reduced side effects compared to nicotinic acid. HM74A has been identified as a high affinity receptor for nicotinic acid whilst HM74 is a lower affinity receptor. The compounds of the present invention may find use as selective HM74A agonists or partial agonists; in which case they will show greater affinity for HM74A than for HM74.

The potential for compounds of formula (I) to activate HM74A may be demonstrated, for example, using the following enzyme and in vitro whole cell assays:

In-vitro testing

For transient transfections, HEK293T cells (HEK293 cells stably expressing the SV40 large T-antigen) were maintained in DMEM containing 10% foetal calf serum and 2mM glutamine. Cells were seeded in 90mm culture dishes and grown to 60-80% confluence (18-24h) prior to transfection. Human HM74A (GenBank™ accession number AY148884) was subcloned in to a mammalian expression vector (pcDNA3; Invitrogen) and transfected using Lipofectamine reagent. For transfection, 9μg of DNA was mixed with 30μl Lipofectamine in 0.6ml of Opti-MEM (Life Technologies Inc.) and was incubated at room temperature for 30min prior to the addition of 1.6ml of Opti-MEM. Cells were exposed to the Lipofectamine/DNA mixture for 5h and 6ml of 20% (v/v) foetal calf serum in DMEM was then added. Cells were harvested 48h after transfection. Pertussis toxin treatment was carried out by supplementation into media at 50ngml^{-1} for 16h. All transient transfection studies involved co-transfection of receptor together with the $G_{i/o}$ G protein, $G_{o1}\alpha$.

For generation of stable cell lines the above method was used to transfect CHO-K1 cells seeded in six well dishes grown to 30% confluence. These cells were maintained in DMEM F-12 HAM media containing 10% foetal calf serum and 2mM glutamine. 48h post-transfection the media was supplemented with 400μg/ml Geneticin (G418, Gibco) for selection of antibiotic resistant cells. Clonal CHO-K1 cell lines stably expressing HM74A were confirmed by [^{35}S]-GTPγS binding measurements, following the addition of nicotinic acid.

P2 membrane preparation - Plasma membrane-containing P2 particulate fractions were prepared from cell pastes frozen at –80°C after harvest. All procedures were carried out at 4°C. Cell pellets were resuspended in 1 ml of 10mM Tris-HCl and 0.1mM EDTA, pH 7.5 (buffer A) and by homogenisation for 20s with a Ultra Turrax followed by passage (5 times) through a 25-gauge needle. Cell lysates were centrifuged at 1,000*g* for 10 min in a microcentrifuge to pellet the nuclei and unbroken cells and P2 particulate fractions were recovered by microcentrifugation at 16,000*g* for 30min. P2 particulate fractions were resuspended in buffer A and stored at –80°C until required.

[^{35}S]-GTPγS binding - assays were performed at room temperature in 384-well format based on methods described previously, (Wieland, T. and Jakobs, K.H. (1994) *Methods Enzymol.* **237,** 3-13). Briefly, the dilution of standard or test compounds were prepared and added to a 384-well plate in a volume of 10μl. Membranes (HM74A or HM74) were diluted in assay buffer (20mM HEPES, 100mM NaCl, 10mM $MgCl_2$, pH7.4) supplemented with saponin

(60μg/ml), Leadseeker WGA beads (Amersham; 250μg/well) and 10μM GDP, so that the 20μl volume added to each well contains 5μg of membranes. [^{35}S]-GTPγS (1170 Ci/mmol, Amersham) was diluted (1:1500) in assay buffer and 20μl added to each well. Following the addition of the radioligand, the plates were sealed, pulse spun and incubated for 4hours at room temperature. At the end of the incubation period the plates were read on a Leadseeker machine (VIEWLUX PLUS; Perkin-Elmer) to determine the levels of specific binding.

In-vivo testing

HM74A agonists were tested in male Spague-Dawley rats (200-250g) which had been fasted for at least 12 hours prior to the study. The compounds were dosed intravenously (5ml/kg) or by oral gavage (10ml/kg). Blood samples (0.3ml tail vein bleed) were taken pre-dose and at three times post-dose (times ranging from 15 minutes to 8 hours post-dose). Each blood sample was transferred to a heparin tube (Becton Dickinson Microtainer, PST LH) and centrifuged (10,000*g* for 5 minutes) to produce a plasma sample. The plasma samples were assayed for levels of non-esterified fatty acids (NEFA) using a commercially available kit (Randox). Inhibition of plasma NEFA levels, relative to pre-dose levels, was used as a surrogate for HM74A agonist activity.

In order to determine whether HM74A compounds exhibited the flushing response associated with nicotinic acid they were dosed to anaesthetised guinea-pigs. Male Dunkin Hartley guinea pigs (300-800g) were fasted for 12 hours prior to being anaesthetised with a mixture of Ketamine hydrochloride (Vetalar, 40mg/kg i.m.), Xylazine (Rompun, 8mg/kg i.m.) and sodium pentobarbitone (Sagatal, 30mg/kg i.p.). Following anaesthesia a tracheostomy was performed and the animals were mechanically ventilated with room air (10-12mL/kg, 60 breaths/min). A jugular vein, and a carotid artery, were cannulated for intravenous administration of test compound and collection of blood respectively. An infra-red temperature probe (Extech Instruments) was placed 3-5mm from the tip of the left ear. Temperature measurements were recorded every minute from 5 minutes prior to test compound and up to 40 minutes post-administration of test compound. Data was automatically collected on a Psion computer before being transferred for data analysis within an Excel spreadsheet. Prior to, and at frequent time points after, compound administration, blood samples (0.3ml) were taken via the carotid arterial cannula and transferred to Microtainer (BD) tubes containing lithium heparin. The samples were mixed thoroughly on a blood roller and then stored on ice prior to centrifugation at 1200g for 5 minutes.

Nicotinic acid (10mg/kg i.v.) produced a mean (± s.e.m.) increase in ear temperature equivalent to 10.42 ± 1.44 (area under curve; arbitary units; n=6). By comparison, the compound of Example 30 (10mg/kg i.v.) produced a mean (± s.e.m.) increase in ear temperature equivalent to 1.52 ± 0.39 (area under curve; arbitary units; n=6), a reduction of 85%.

Compounds according to Formula (I) have been synthesised (see synthetic examples below) and tested in one or more of the assays discussed above. All of the exemplified compounds have a pEC50 of 4.9 (+/- 0.3 log unit) or greater and an efficacy of 30% or greater. Some particular compounds are exemplified below.

General purification and analytical methods:

The mass spectra (MS) were recorded on a Fisons VG Platform mass spectrometer using electrospray positive ionisation [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative ionisation [(ES-ve to give $(M-H)^-$ molecular ion] modes.

^1H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard.

Biotage™ chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil.

Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (5cm x 10mm i.d.) with 0.1% HCO_2H in water and 95% MeCN, 5% water (0.5% HCO_2H) utilising the following gradient elution conditions: 0-1.0 minutes 5%B, 1.0-8.0 minutes 5→30%B, 8.0-8.9 minutes 30%B, 8.9-9.0 minutes 30→95%B, 9.0-9.9 minutes 95%B, 9.9-10 minutes 95→0%B at a flow rate of 8ml $minutes^{-1}$ (System 2). The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

Preparative h.p.l.c. refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5µm column (10cm x 21.2mm i.d.) with 0.1% HCO_2H in water (A) and MeCN (0.5% HCO_2H) (B) utilising the generic gradient elution conditions expressed as "x to y" gradient with a gradient system as follows: 0-1.45minutes x%B, 1.45-20 minutes x→y%B, 20-24 minutes y→95%B, 24-30 minutes 95%B, 32-34 minutes 95→x%B at a flow rate of 8ml $minutes^{-1}$. The Gilson 233 fraction collector was triggered by UV (254nm).

SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd.

Strata Phenyl SPE refers to the use of cartridges sold by Phenomenex. The compound was loaded onto a cartridge previously conditioned with MeCN and equilibrated with 5% MeCN in water. The compound was eluted with 0.1% HCO_2H in water and MeCN (0.5% HCO_2H) in a suitable gradient on a Combiflash Optix 10.

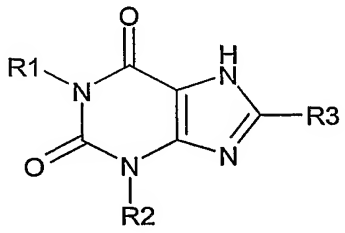
As indicated above, compounds of Formula (I) may find use in human or veterinary medicine, in particular as activators of HM74A, in the management of dyslipidaemia and hyperlipoproteinaemia.

Thus, there is provided as a further aspect of the present invention a compound of formula (I) or a physiologically functional derivative thereof, for use in human or veterinary medicine, particularly in the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

There is provided as a further aspect of the present invention a compound of formula (I) or a physiologically functional derivative thereof, for use in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity. As such, the compounds are also provided for use in the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke.

It will be appreciated that references herein to treatment extend to prophylaxis, prevention of recurrence and suppression of symptoms as well as the treatment of established conditions.

According to another aspect of the invention, there is provided the use of a compound of formula (II)



and physiologically functional derivative thereof, wherein:

R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3;

R^2 is selected from: C_{2-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl;
and R^3 is selected from halogen and CN;

in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia. In particular, the use is provided of a compound of Formula (II) in the manufacture of a medicament for the treatment of diabetic dyslipidaemia or mixed dyslipidaemia, heart failure, hypercholesteraemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, stroke and cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia.

In one embodiment of the invention, there is provided a compound of formula (II) for use in the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia. In particular, the use is provided of a compound of Formula (II) in the manufacture of a medicament for the treatment of diabetic dyslipidaemia or mixed dyslipidaemia, heart failure, hypercholesteraemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, stroke and cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia.

In particular embodiments, R^1 is selected from: hydrogen, C_{1-4} alkyl, CH_2CN and $(CH_2)_3CF_3$. In more particular embodiments R^1 is selected from: hydrogen and methyl.

In certain embodiments R^2 is selected from: C_{3-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl. Particularly, R^2 is selected from: C_{3-10} unsubstituted alkyl, C_{1-6}alkyl with one or more CN substitutions, C_{1-10} alkyl with one or more fluorine substitutions, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl. More particularly R^2 is selected from: C_{3-10} unsubstituted alkyl; $(CH_2)_{1-5}CN$; C_{2-5} alkyl with one or more fluorine substitutions; C_5 alkenyl; and C_{1-4} alkyl substituted with cycloalkyl. Most particularly R^2 is selected from C_{4-6} unsubstituted n-alkyl, for example pentyl; $(CH_2)_{1-3}CN$, for example, $(CH_2)CN$ or $(CH_2)_3CN$; C_{3-4} alkyl with one or more fluorine substitutions, in particular where the terminal carbon is fully saturated with fluorine, for example $(CH_2)_{2-3}CF_3$; and C_5 alkenyl, in particular, where there is only one double bond, for example where the double bond is located between the fourth and fifth carbons (terminal alkenyl).

In particular embodiments, R^3 represents halogen. More particularly, R^3 is selected from chlorine and bromine. Most particularly, R^3 represents chlorine.

Particular compounds for use in the treatment of, or in the manufacture of a medicament for the treatment of disorders of lipid metabolism including dislipidaemia or hyperlipoproteinaemia include:

(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)acetonitrile,
3-Butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Bromo-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-1-propyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
3-Butyl-8-chloro-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione,
(3-Butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile,
8-Chloro-3-(2-cyclopropylethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
4-(8-Chloro-1-methyl-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile,
8-Chloro-1-ethyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
1-Methyl-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile,
8-Chloro-3-propyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3-methylbutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione,
3-Butyl-1-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile,
8-Chloro-3-(4-penten-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-hexyl-3,7-dihydro-1*H*-purine-2,6-dione,
4-(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile,
8-Chloro-3-hexyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione,
3-Butyl-8-chloro-1-ethyl-3,7-dihydro-1*H*-purine-2,6-dione,
[8-Chloro-3-(2-cyclopropylethyl)-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl]acetonitrile,
(8-Chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile,
8-Chloro-1-(4,4,4-trifluorobutyl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
2,2'-(8-Chloro-2,6-dioxo-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl)diacetonitrile,
8-Chloro-1-methyl-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(2-cyclohexylethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
1,3-Dibutyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile,
1,3-Dibutyl-8-iodo-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(4-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(6-methylheptyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-octyl-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-decyl-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclohexylmethyl)-3,7-dihydro-1H-purine-2,6-dione,

(+/-)-8-Chloro-3-(3-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(2-cyclopentylethyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclopropylmethyl)-3,7-dihydro-1H-purine-2,6-dione,
(+/-)-8-Chloro-3-(2-methylbutyl)-3,7-dihydro-1H-purine-2,6-dione,
(+/-)-8-Chloro-3-(2-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclobutylmethyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(cyclopentylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3-cyclopropylpropyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(2-cyclobutylethyl)-3,7-dihydro-1H-purine-2,6-dione,
8-Chloro-3-(4-fluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(3-fluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione,
8-Chloro-3-(5-fluoropentyl)-3,7-dihydro-1*H*-purine-2,6-dione,
4-(8-Chloro-1-methyl-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile,
3-(3-Buten-1-yl)-8-chloro-3,7-dihydro-1H-purine-2,6-dione,
6-(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)-2,2-dimethylhexanenitrile,
8-Chloro-3-(6-fluorohexyl)-3,7-dihydro-1H-purine-2,6-dione,
8-chloro-3-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione.

It is to be understood that this aspect of the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described herein above for compounds of Formula (II).

Additionally, the present invention provides the use of a compound of formula (I) or a physiologically functional derivative thereof, in the manufacture of a medicament for the treatment of inflammatory diseases or conditions of the joint, particularly arthritis (e.g. rheumatoid arthritis, osteoarthritis, prosthetic joint failure), or of the gastrointestinal tract (e.g. ulcerative colitis, Crohn's disease, and other inflammatory bowel and gastrointestinal diseases, gastritis and mucosal inflammation resulting from infection, the enteropathy provoked by non-steroidal anti-inflammatory drugs), of the lung (e.g. adult respiratory distress syndrome, asthma, cystic fibrosis, or chronic obstructive pulmonary disease), of the heart (e.g. myocarditis), of nervous tissue (e.g. multiple sclerosis), of the pancreas, (e.g. inflammation associated with diabetes melitus and complications thereof, of the kidney (e.g. glomerulonephritis), of the skin (e.g. dermatitis, psoriasis, eczema, urticaria, burn injury), of the eye (e.g. glaucoma) as well as of transplanted organs (e.g. rejection) and multi-organ diseases (e.g. systemic lupus erythematosis, sepsis) and inflammatory sequelae of viral or bacterial infections and inflammatory conditions associated with atherosclerosis and following hypoxic or ischaemic insults (with or without reperfusion), for example in the brain or in ischaemic heart disease.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with a condition where under-activation of the HM74A receptor contributes to

the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Again, it is to be understood that this aspect of the present invention includes any combination of particular embodiments and covers all combinations of particular substituents described herein above for compounds of Formula (I).

More particularly, the present invention provides a method for the treatment of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, which method comprises administering to said human or animal subject an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof. As such, these compounds may also find favour in methods for the treatment of coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease and stroke, which methods comprise administering to said human or animal subject an effective amount of a compound of formula (I).

The amount of a HM74A modulator which is required to achieve the desired biological effect will, of course, depend on a number of factors, for example, the mode of administration and the precise clinical condition of the recipient. In general, the daily dose will be in the range of 0.1mg - 1g/kg, typically 0.1 - 100mg/kg. An intravenous dose may, for example, be in the range of 0.01mg to 0.1g/kg, typically 0.01mg to 10mg/kg, which may conveniently be administered as an infusion of from 0.1μg to 1mg, per minute. Infusion fluids suitable for this purpose may contain, for example, from 0.01μg to 0.1mg, per millilitre. Unit doses may contain, for example, from 0.01μg to 1g of a HM74A modulator. Thus ampoules for injection may contain, for example, from 0.01μg to 0.1g and orally administrable unit dose formulations, such as tablets or capsules, may contain, for example, from 0.1mg to 1g. No toxicological effects are indicated/expected when a compound of the invention is administered in the above mentioned dosage range.

A compound of the present invention may be employed as the compound *per se* in the treatment of a disease where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, an example of this is where a compound of the present invention is presented with an acceptable carrier in the form of a pharmaceutical formulation. The carrier must, of course, be acceptable in the sense of being compatible with the other ingredients of the formulation and must not be deleterious to the recipient. The carrier may be a solid or a liquid, or both, and may be formulated with the HM74A modulator as a unit-dose formulation, for example, a tablet, which may contain from 0.05% to 95% by weight of the HM74A modulator.

The formulations include those suitable for oral, rectal, topical, buccal (e.g. sub-lingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration.

There is also provided according to the invention a process for preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Formulations suitable for oral administration may be presented in discrete units, such as capsules, cachets, lozenges or tablets, each containing a predetermined amount of a HM74A modulator; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. In general, the formulations are prepared by uniformly and intimately admixing the active HM74A modulator with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet may be prepared by compressing or moulding a powder or granules of the HM74A modulator optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Moulded tablets may be made by moulding, in a suitable machine, the powdered compound moistened with an inert liquid diluent.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p-hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a HM74A modulator in a flavoured base, usually sucrose and acacia or tragacanth, and

pastilles comprising the HM74A modulator in an inert base such as gelatin and glycerin or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of an HM74A modulator, the formulation may be isotonic with the blood of the intended recipient. These preparations could be administered intravenously, although administration may also be effected by means of subcutaneous, intramuscular, or intradermal injection. Such preparations may conveniently be prepared by admixing the HM74A modulator with water and rendering the resulting solution sterile and isotonic with the blood. Injectable compositions according to the invention will generally contain from 0.1 to 5% w/w of the HM74A modulator.

Thus, formulations of the present invention suitable for parenteral administration comprising a compound according to the invention may be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multi-dose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or toxicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

Formulations suitable for rectal administration may be presented as unit-dose suppositories. These may be prepared by admixing a HM74A modulator with one or more conventional solid carriers, for example, cocoa butter or glycerides and then shaping the resulting mixture.

Formulations suitable for topical application to the skin may take the form of an ointment, cream, lotion, paste, gel, spray, aerosol, or oil. Carriers which may be used include vaseline, lanolin, polyethylene glycols, alcohols, and combinations of two or more thereof. The HM74A modulator is generally present at a concentration of from 0.1 to 15% w/w of the composition, for example, from 0.5 to 2%.

By topical administration as used herein, we include administration by insufflation and inhalation. Examples of various types of preparation for topical administration include ointments, creams, lotions, powders, pessaries, sprays, aerosols, capsules or cartridges for use in an inhaler or insufflator or drops (e.g. eye or nose drops).

Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents and/or solvents. Such bases may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such

as arachis oil or castor oil or a solvent such as a polyethylene glycol. Thickening agents which may be used include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, microcrystalline wax and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents or thickening agents.

Powders for external application may be formed with the aid of any suitable powder base, for example, talc, lactose or starch. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, solubilising agents or suspending agents.

Spray compositions may be formulated, for example, as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, 1,1,1,2,3,3,3-heptafluoropropane, 1,1,1,2- tetrafluorethane, carbon dioxide or other suitable gas.

Capsules and cartridges for use in an inhaler or insufflator, of for example gelatin, may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example in combination with other classes of dyslipidaemic drugs (e.g. statins, fibrates, bile-acid binding resins or nicotinic acid).

The compounds of the instant invention may be used in combination with one or more other therapeutic agents for example in combination with other classes of dyslipidaemic drugs e.g. 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) or fibrates or bile acid binding resins or nicotinic acid. The invention thus provides, in a further aspect, the use of such a combination in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial and the use of a compound of formula (I) or (II) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof in the manufacture of a medicament for the combination therapy of disorders of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia such as diabetic dyslipidaemia and mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa or obesity.

When the compounds of the present invention are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above optimally together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When combined in the same formulation it will be appreciated that the two components must be stable and compatible with each other and the other components of the formulation and may be formulated for administration. When formulated separately they may be provided in any convenient formulation, conveniently in such a manner as are known for such compounds in the art.

When in combination with a second therapeutic agent active against the same disease, the dose of each component may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or (II) or a physiologically acceptable salt or solvate thereof together with another therapeutically active agent.

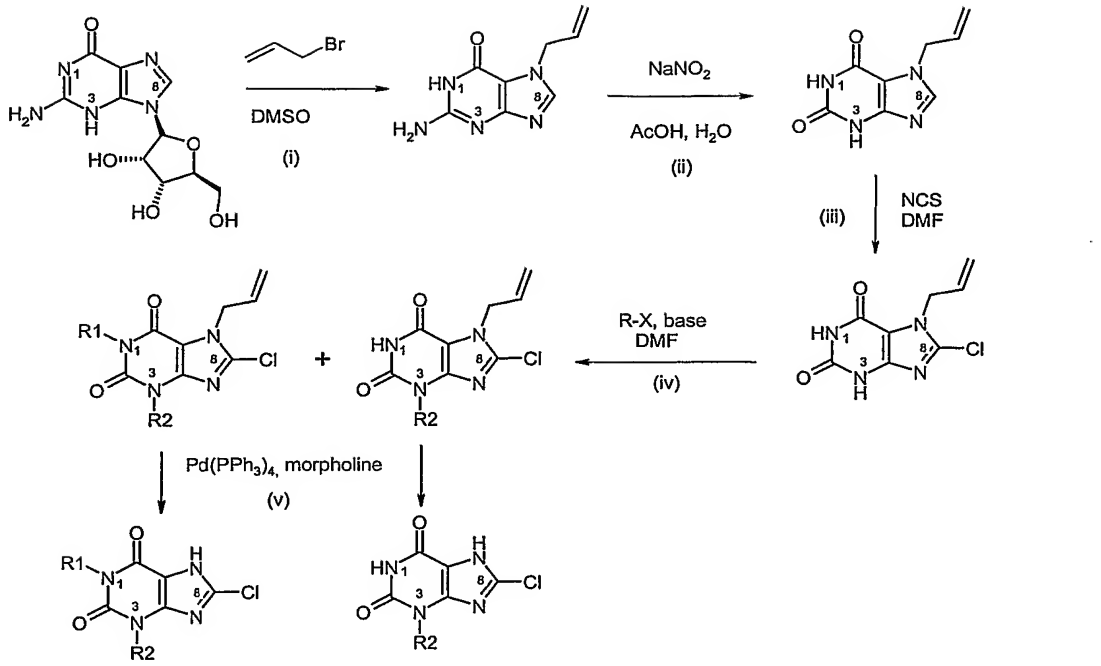
The combination referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier thereof represent a further aspect of the invention.

The compounds of the present invention have useful duration of action.

The compounds of the present invention and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting a further aspect of this invention.

Process A:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^1 is H or is the same as R^2 and R^3 is Cl, comprises:



i) Alkylation of guanine with allyl bromide

ii) Diazotisation with sodium nitrite followed by hydrolysis to form the xanthine

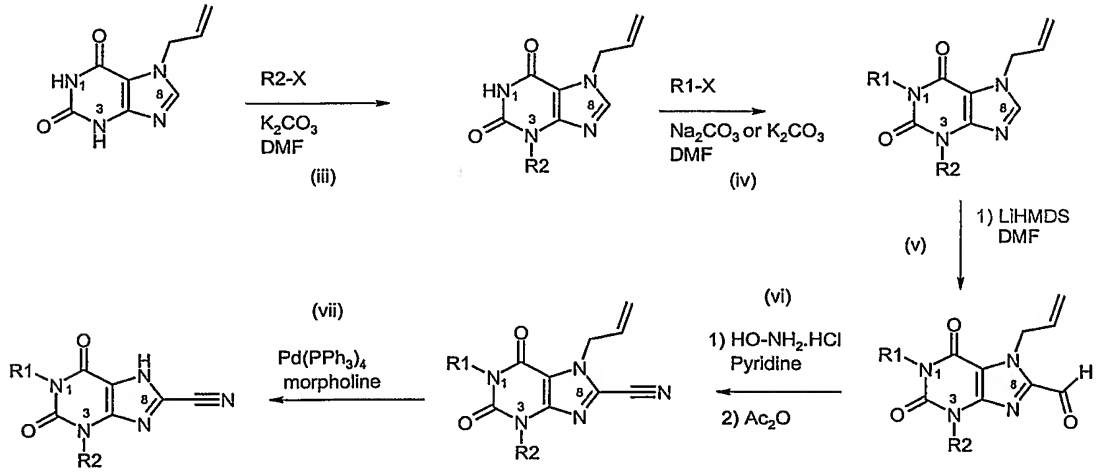
iii) Chlorination

iv) Alkylation at N3 and/or dialkylation at N1 and N3

v) Palladium catalysed removal of the allyl group

Process B:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^3 is CN comprises steps (i) and (ii) of Process A followed by:



iii) Alkylation at N3

iv) Alkylation at N1

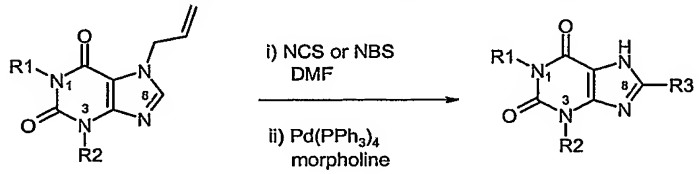
v) Formation of aldehyde at C8 by lithiation with LiHMDS and DMF quench

vi) Conversion of the aldehyde to the nitrile

vii) Palladium catalysed removal of the allyl group

Process C:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^3 is Cl or Br comprises steps (i) to (iv) of Process B followed by:



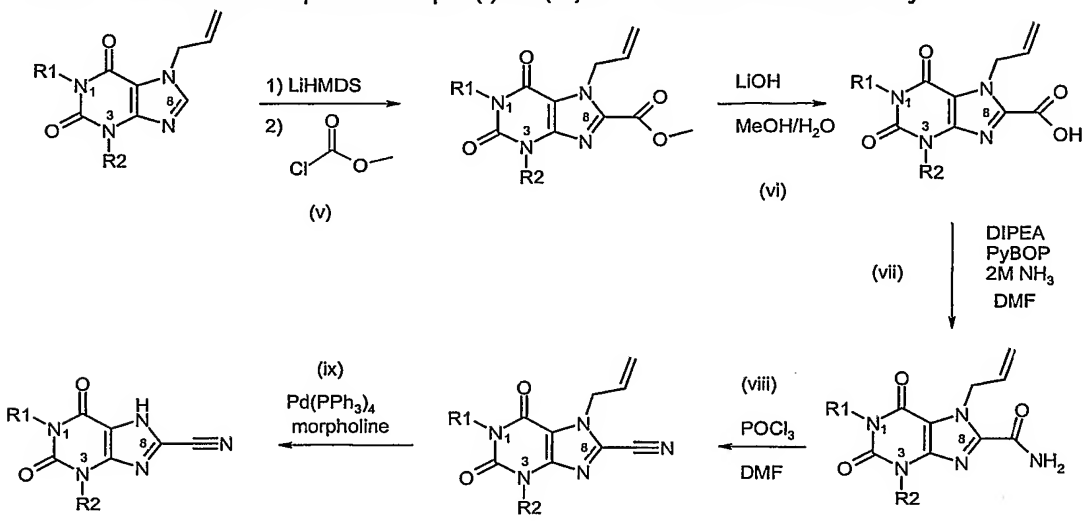
R3 = Cl or Br

i) Halogenation at C8 using NCS or NBS

ii) Palladium catalysed removal of the allyl group

Process D:

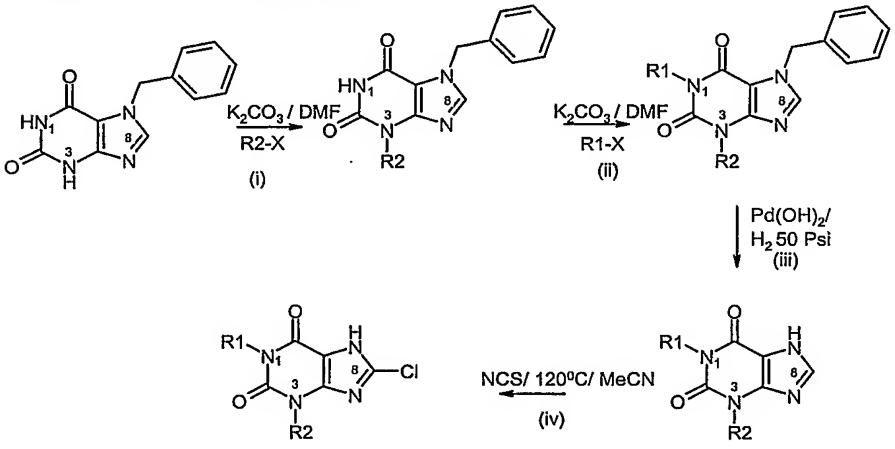
A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^3 is CN comprises steps (i) to (iv) of Process B followed by:



v) Formation of ester
vi) Hydrolysis of the methyl ester
vii) Conversion of the acid to the amide.
viii) Conversion of the amide to the nitrile
ix) Palladium catalysed removal of the allyl group

Process E:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^3 is Cl comprises:

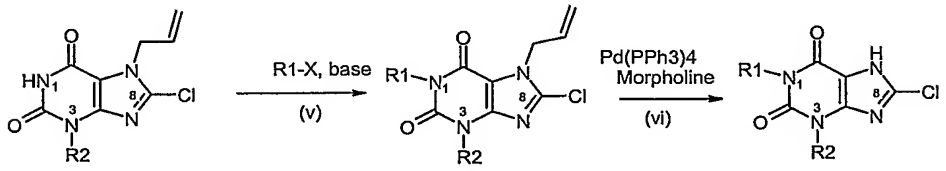


i) Alkylation at N3
ii) Alkylation at N1
iii) Debenzylation

iv) Chlorination at C8

Process F:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^1 differs from R^2 and R^3 is Cl comprises steps (i) to (iv) of Process A followed by:

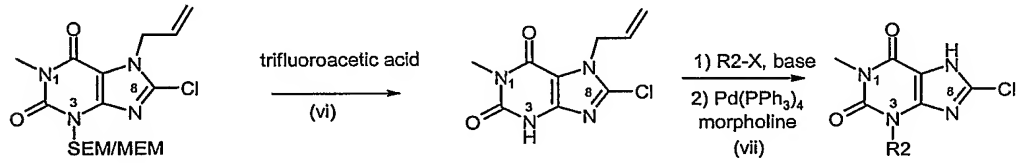


v) Alkylation at N1

vi) Palladium catalysed removal of the allyl group

Process G:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^1 differs from R^2 and R^3 is Cl comprises steps (i) to (v) of Process F (where R^2 from process F is specifically SEM or MEM) followed by:

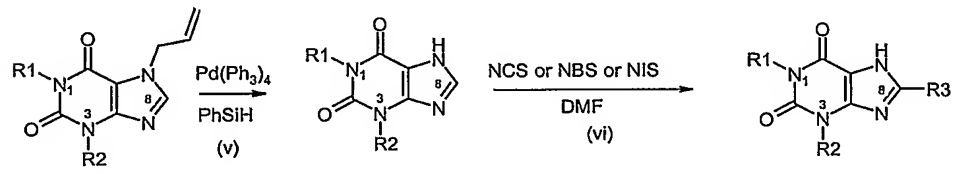


vi) Cleavage of MEM or SEM protecting group group

vii) Alkylation of N3 followed by palladium catalysed removal of the allyl group

Process H:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^3 is Cl, Br, I or F comprises steps (i) to (iv) of Process B followed by:

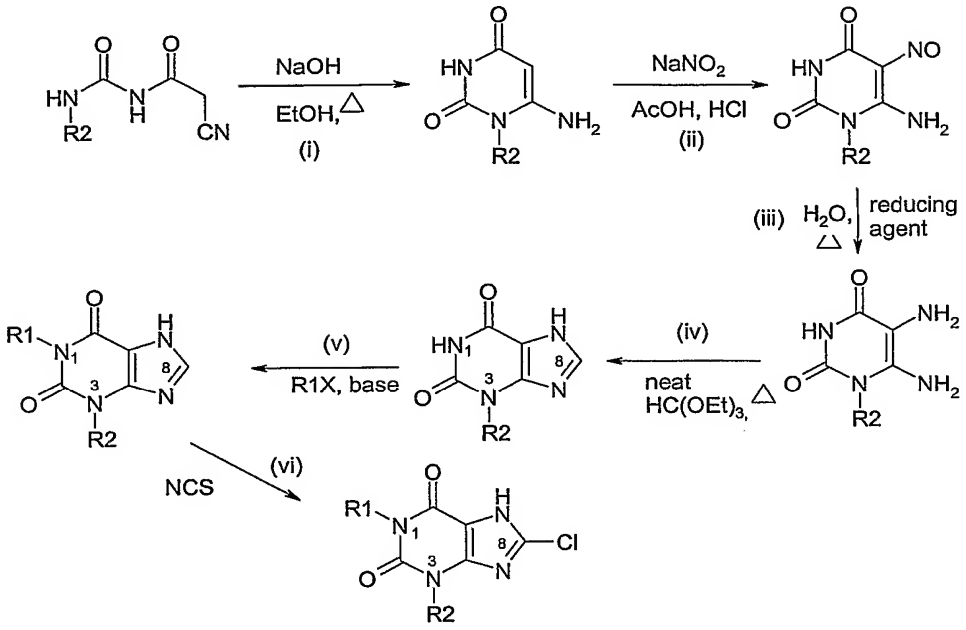


v) Palladium catalysed removal of allyl group

vi) Halogenation at C8 using NCS, NBS or NIS

Process I:

A process according to the invention for preparing a compound of formula (I) or formula (II) in which R^1 is H or alkyl, R^2 is alkyl and R^3 is Cl comprises:



i) Pyrimidinedione formation
ii) Nitrosation
iii) Reduction using $Na_2S_2O_4$ or a similar reducing agent
iv) Xanthine formation
v) Alkylation at N1 (optional)
vi) Halogenation at C8 using NCS

Where desired or necessary, as a final stage in any of the above synthetic processes, a resultant compound of formula (I) or (II) can be converted into a physiologically acceptable salt form or vice versa or converting one salt form into another physiologically acceptable salt form.

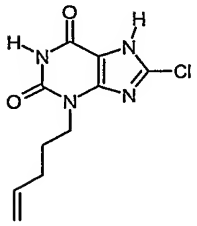
ABBREVIATIONS

THF	Tetrahydrofuran
Ac	Acetyl
DCM	Dichloromethane
DMEM	Dulbecco's Modified Eagle's Medium
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulphonic acid
DMSO	Dimethylsulphoxide
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NIS	N-iodosuccinimide
DMF	Dimethylformamide
LiHMDS	Lithium hexamethyldisilylamide
DBAD	Dibenzylazodicarboxylate
DIPEA	Diisopropylethylamine
PyBOP	Benzotriazo-1-yloxytripyrrolidinophosphonium hexafluorophosphate
MEM	Methoxyethyloxymethyl
SEM	2-(trimethylsilyl)ethoxymethyl
TFA	Trifluoroacetic acid
RT	room temperature
$\triangle$	Heat

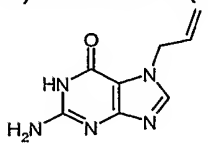
The following non-limiting examples illustrate the present invention:

Synthetic Examples

Example 1: 8-Chloro-3-(4-penten-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione

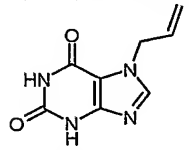


a) 2-amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one



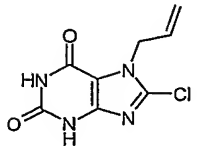
A mixture of guanosine (20g, 0.071mol), allyl bromide (14.7ml, 0.169mol) and anhydrous DMSO (100ml) was stirred at rt, under nitrogen, for 18 hours. Concentrated HCl (50ml of 37%) was added in one portion and the mixture stirred for 45 minutes then poured into MeOH (600ml). The methanolic solution was neutralised with 2M NaOH(aq) solution and the resulting white precipitate collected by filtration. The white solid was dried under vacuum at 50°C for 18 hours to afford the title compound (16g crude, 119%). m/z 192.2[MH^+].

b) 7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



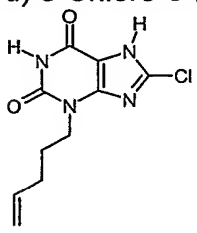
A mixture of 2-amino-7-(2-propen-1-yl)-1,7-dihydro-6*H*-purin-6-one (40g, 0.209mol) in AcOH (900ml) and water (100ml) was heated at 55°C. Sodium nitrite (57.74g, 0.837mol) in water (100ml) was added dropwise. Care; toxic fumes. After the addition was complete (approximately 25 minutes) the reaction mixture was allowed to cool to ambient temperature and then concentrated to approximately 1/3 of its original volume. Water (500ml) was added and the resulting precipitate collected by filtration. The residue was washed with water then dried at 50°C over P_2O_5 and under vacuum for 2 hours to give the title compound (17.20g). The aqueous fraction was concentrated and water added (100ml). Again the resulting solid was filtered and dried. This gave more of the title compound (2.31g). Combined product (19.52g, 49%). m/z 193.2[MH^+].

c) 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



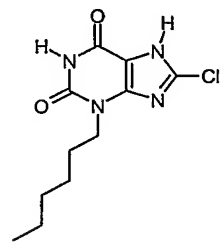
To a solution of 7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione) (10.52g, 54.7mmol) in anhydrous DMF (60ml) was added NCS (8.04g, 60.2mmol). The reaction mixture was left to stir under nitrogen at 20°C for 6 hours. The reaction mixture was concentrated *in vacuo* to give an amber oil. MeOH was added and left to stand for 18 hours. The resulting residue was filtered and dried under vacuum to give the title compound (7.69g, 62%). m/z 227.2[MH^+].

d) 8-Chloro-3-(4-penten-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



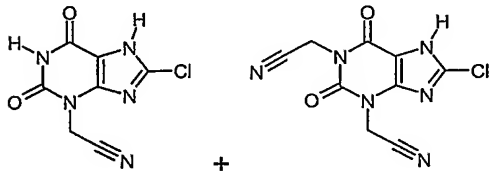
8-Chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.10g, 0.44mmol) was dissolved in DMF (1.5ml) containing sodium carbonate (0.12g, 0.49mmol) and 5-bromopentene (0.07g, 0.49mmol) and the mixture stirred for 18h. On completion of alkylation, morpholine (0.5ml) and tetrakis(triphenylphosphine) palladium (0) (0.08g, 0.07mmol) were added and stirring continued for 3.5h. The reaction was diluted with ethyl acetate (10ml) washed sequentially with 2N hydrochloric acid (2x5ml) and brine (3x5ml) and the organic isolated, dried ($MgSO_4$) and concentrated. The crude product was suspended in methanol (2ml) and purified on an aminopropyl SPE (5g) eluting with methanol first then 5%acetic acid in methanol to elute the title compound which was isolated as a white solid after concentration (0.039g, 35%). NMR; (400MHz, d^6-DMSO) 1.75 (m, 2H), 2.05 (m, 2H), 3.85 (t, 2H, J=7Hz), 4.95 (m, 1H), 5.05 (m, 1H), 5.8 (m, 1H), 11.1 (br s, 1H), one exchangeable proton not observed to δ_H 13; m/z 255[MH^+]

Example 2: 8-Chloro-3-hexyl-3,7-dihydro-1*H*-purine-2,6-dione

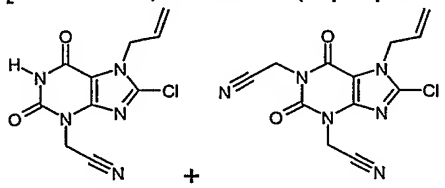


Prepared in similar fashion to Example 1 using hexyl iodide, to afford the title compound. NMR; δ_H (400MHz, d^6-DMSO) 0.85 (t, 3H, J=7Hz), 1.25 (br s, 6H), 1.6 (m, 2H), 3.85 (t, 2H, J=8Hz), 11.2 (br. s, 1H), one exchangeable proton not observed to δ_H 13; m/z 271[MH^+]

Examples 3 and 4: (8-chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)acetonitrile and 2,2'-(8-chloro-2,6-dioxo-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl)diacetonitrile



a) [8-chloro-2,6-dioxo-7-(2-propen-1-yl)-1,2,6,7-tetrahydro-3*H*-purin-3-yl]acetonitrile and 2,2'-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl]diacetonitrile

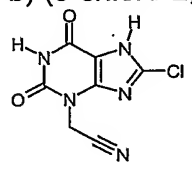


A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.445g, 2.0mmol) in DMF (8ml) was treated with sodium carbonate (0.18g, 1.7mmol) and bromoacetonitrile (0.1ml, 1.4mmol). The stirred mixture was heated at 70°C for 3 hours then cooled to 50°C and treated with further bromoacetonitrile (0.06ml, 0.8 mmol). The mixture was maintained at 50°C for a further 2 hours and then cooled to ambient temperature and evaporated to dryness. The residue was treated with 1M aqueous hydrochloric acid (20ml) and extracted with ethyl acetate (2x50ml). The organic fractions were combined, dried over magnesium sulfate, filtered and evaporated. The residue was dissolved in dichloromethane (2ml), after 20 minutes, the resulting precipitated solid (unreacted 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione was filtered off and washed with further dichloromethane). The filtrate was concentrated *in vacuo* and subjected to flash chromatography using ethyl acetate/cyclohexane as eluant in a gradient elution from 1:3 to 4:1. To afford the two title compounds:

[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-1,2,6,7-tetrahydro-3*H*-purin-3-yl]acetonitrile
White solid (0.084g, 16%); m/z 266 [MH^+].

2,2'-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl]diacetonitrile
White solid (0.195g, 32%); m/z 305 [MH^+].

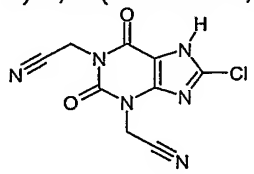
b) (8-chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)acetonitrile



A solution of [8-chloro-2,6-dioxo-7-(2-propen-1-yl)-1,2,6,7-tetrahydro-3*H*-purin-3-yl]acetonitrile (0.084g, 0.32mmol) in THF (5ml) was degassed by the successive application of vacuum and nitrogen pressure to the reaction mixture. The solution was subsequently treated with morpholine (0.3ml, 3.4mmol) and tetrakis(triphenylphosphine)palladium(0)

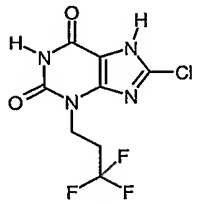
(0.03g, 0.03mmol). After 2 hours, the mixture was treated with 2M aqueous hydrochloric acid (3ml) and chloroform (5ml). The mixture was separated and the organic phase evaporated. The product was purified from the residue using mass-directed HPLC, to afford the title compound as a white solid (0.018g, 25%). NMR δ_H (400MHz, d^6-DMSO) 4.95 (s, 2H), 11.49 (s, 1H), 14.63 (br. s, 1H); m/z 226 [MH^+].

c) 2,2'-(8-chloro-2,6-dioxo-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl)diacetonitrile



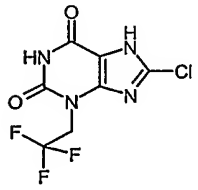
The title compound was prepared from 2,2'-[8-chloro-2,6-dioxo-7-(2-propen-1-yl)-6,7-dihydro-1*H*-purine-1,3(2*H*)-diyl]diacetonitrile using the conditions described for the synthesis of (8-chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)acetonitrile.
To afford the title compound as a white solid 0.06g (4%); NMR δ_H (400MHz, d^6-DMSO) 4.88 (s, 2H), 5.06 (s, 2H), NH not observed to δ_H 14; m/z 282 [MNH_4^+].

Example 5: 8-chloro-3-(3,3,3-trifluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione



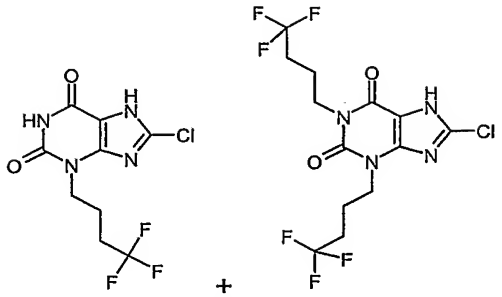
Prepared in similar fashion to Example 3 using 3-bromo-1,1,1-trifluoropropane as alkylating agent to afford title compound.
NMR δ_H (400MHz, d^6-DMSO) 2.64-2.76 (m, 2H), 4.12 (t, 2H, J=7Hz), 11.30 (s, 1H), 14.46 (br. s, 1H); m/z 283 [MH^+]

Example 6: 8-chloro-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione

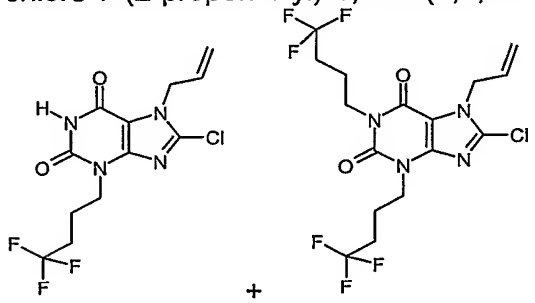


Prepared in similar fashion to Example 3 using 2-bromo-1,1,1-trifluoroethane as the alkylating agent and sodium bicarbonate as base to afford title compound.
δ_H (400MHz, d^4-MeOD) 4.68 (q, 2H, J=8.5Hz); m/z 267.1 [M-H]$^-$

Example 7 and 8: 8-chloro-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione and 8-chloro-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



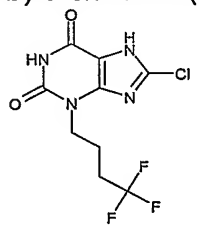
a) 8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione and 8-chloro-7-(2-propen-1-yl)-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione(1.5g, 6.64 mmol), sodium carbonate (844mg, 7.9 mmol) and 4-bromo-1,1,1-trifluorobutane (1.39g, 7.3 mmol) were stirred in dimethylformamide (25ml, dry) for seven days. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated and washed with hydrochloric acid (2N), brine, dried ($MgSO_4$) and then evaporated to dryness. The crude product was triturated with ether and the solid collected by filtration to afford 8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione as a white solid (1.23g, 57%). m/z 337 [MH^+].

The reduced filtrate was chromatographed on silica, SPE column (20g). Elution with cyclohexane:ethylacetate (10:1 to 2:1) afforded 8-chloro-7-(2-propen-1-yl)-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione as a syrup (480mg, 16%). m/z 447 [MH^+].

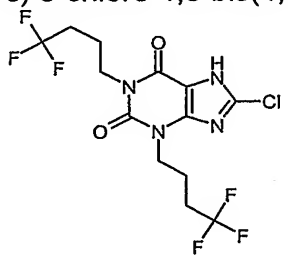
b) 8-chloro-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



8-chloro-7-(2-propen-1-yl)-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione (84mg, 0.25 mmol) and morpholine (220ul, 2.5mmol) were degassed with nitrogen in tetrahydrofuran (3ml) and then tetrakis(triphenylphosphine)palladium(0) (29mg, 0.025 mmol) was added and the reaction stirred at room temperature overnight. The white precipitate was collected by filtration and washed with tetrahyrofuran and ether to afford the morpholine

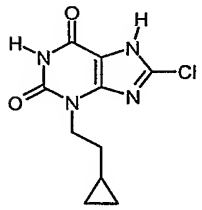
salt of the title compound (59mg). This was treated with 2N HCl and methanol and the solvents evaporated to dryness before re-dissolving in DMSO / MeOH and purifying by preparative HPLC using a 10 to 40% gradient to give the title compound (11mg, 14.9%). NMR δ_H (400MHz, d^4-MeOD) 1.92-2.03 (m, 2H), 2.19-2.33 (m, 2H), 4.06 (t, 2H, J=7Hz); m/z 297 [MH^+].

c) 8-chloro-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione

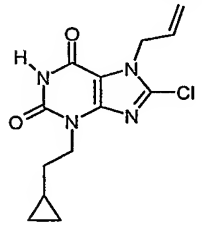


8-chloro-7-(2-propen-1-yl)-1,3-bis(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione (478mg, 1.1 mmol) and morpholine (937ul, 11mmol) were degassed with nitrogen in tetrahydrofuran (10ml) and then tetrakis(triphenylphosphine)palladium(0) (123mg, 0.11 mmol) was added and the reaction stirred at room temperature overnight. The reaction mixture was partitioned between dichloromethane and hydrochloric acid 2N. The organic phase was separated and reduced to give the crude product. This was purified by aminopropyl SPE (5g) followed by re-crystallisation from acetonitrile to afford the title compound (75.5mg, 16.9%). NMR. δ_H (400MHz, $CDCl_3$) 1.96-2.13 (m, 4H), 2.15-2.29 (m, 4H), 4.15-4.23 (m, 4H), 12.94 (br. s, 1H); m/z 407 [MH^+].

Example 9: 8-chloro-3-(2-cyclopropylethyl)-3,7-dihydro-1*H*-purine-2,6-dione



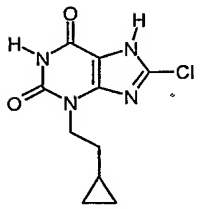
a) 8-chloro-3-(2-cyclopropylethyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione(1.5g, 6.64 mmol), sodium carbonate (844mg, 7.9 mmol) and 2-cyclopropylethyl methanesulfonate (1.19g, 7.3 mmol) were stirred in dimethylformamide (25ml, dry) for two days at 80°C. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was separated and

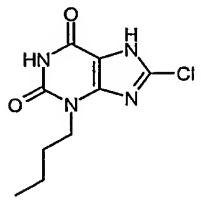
washed with hydrochloric acid (2N), brine, dried ($MgSO_4$) and then evaporated to dryness. The crude product was triturated with ether and the solid collected by filtration to afford the title compound as a white solid (0.96g, 49%). m/z 295 [MH^+].

b) 8-chloro-3-(2-cyclopropylethyl)-3,7-dihydro-1*H*-purine-2,6-dione

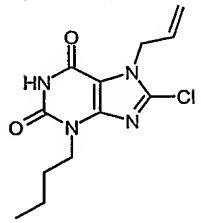


8-chloro-3-(2-cyclopropylethyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (74mg, 0.25 mmol) and morpholine (220ul, 2.5mmol) were degassed with nitrogen in tetrahydrofuran (3ml) and then tetrakis(triphenylphosphine)palladium(0) (29mg,0.025 mmol) was added and the reaction stirred at room temperature overnight. The white precipitate was collected by filtration and washed with tetrahyrofuran and ether to afford the morpholine salt of the title compound (52mg). This was treated with 2N HCl and methanol and the solvents evaporated to dryness before re-dissolving in DMSO / MeOH and purifying by preparative HPLC using a 10 to 40% gradient to give the title compound (22mg, 34.6%). NMR δ_H (400MHz, d^4-MeOD) 0.00-0.05 (m, 2H), 0.37-0.43 (m, 2H), 0.67-0.77 (m, 1H), 1.61 (q, 2H, J=7Hz), 4.06-4.11 (m, 2H); m/z 255 [MH^+].

Example 10: 3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione



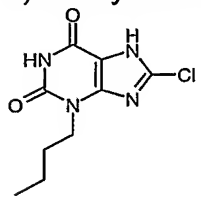
a) 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.34g, 13.4mmol) in anhydrous DMF (19ml) was added NCS (1.97g, 14.8mmol) and left to stir at rt under nitrogen for 22 hours. The mixture was concentrated *in vacuo* to give a yellow solid which was filtered and washed with methanol. The filtrate was concentrated and the process repeated. On the final wash the filtrate was purified by SPE (Si, 20g) cartridge eluting with

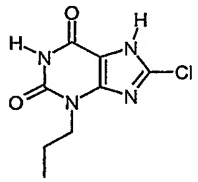
1:1; EtOAc:cyclohexane. The combined solids were dried under vacuum to afford the title compound (2.42g, 64%); m/z 283.3[MH^+]

b) 3-butyl-8-chloro-3,7-dihydro-1*H*-purine-2,6-dione



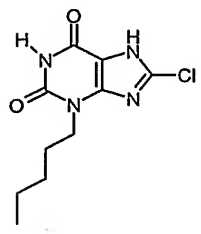
A solution of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.35mmol) in anhydrous THF (4ml) and anhydrous DMSO (0.4ml) was treated with $Pd(PPh_3)_4$ (61mg, 0.053mmol). The mixture was degassed under gentle vacuum, morpholine (308uL, 3.5mmol) was added, and left to stir at rt under nitrogen for 4 hours. The yellow solution was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up in MeOH and passed down an amino-propyl SPE (5g), eluting with MeOH followed by 5%AcOH/ MeOH. The product fractions were combined and concentrated *in vacuo* to afford the title compound as an off white solid (30mg, 35%). NMR; δ_H (400MHz, d^6-DMSO) 0.89 (t, 3H, J=7.5Hz), 1.23-1.34 (m, 2H), 1.55-1.65 (m, 2H), 3.85 (t, 2H, J=7Hz), 11.17 (s, 1H), 14.37 (br.s, 1H); m/z 243.3[MH^+].

Example 11: 8-Chloro-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione

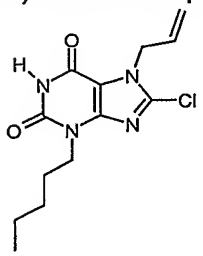


3-Propyl-3,7-dihydro-1*H*-purine-2,6-dione (J.Med.Chem, 1993, 36 (10), 1380-6)(0.3g, 1.5mmol) and N-chlorosuccinimide (0.21g, 1.5mmol) were dissolved in DMF (5ml) and the solution stirred for 5h. The solution was concentrated and the solid residues washed with methanol and filtered to provide the product as a white solid (0.148g, 42%). NMR; δ_H (400MHz, d^6-DMSO) 0.85 (t, 3H, J=7Hz), 1.65 (m, 2H), 3.8 (t, 2H, J=7Hz), 11.2 (s, 1H), one exchangeable not observed to δ_H 13; m/z 229[MH^+]

Example 12: 8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

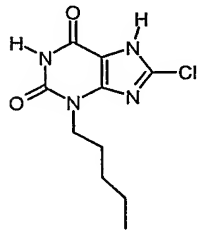


a) 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



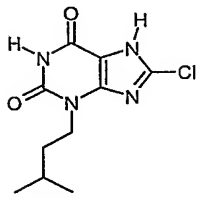
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.44mmol) in anhydrous DMF (3ml) was added sodium carbonate (0.051g, 0.484mmol). After 10 minutes stirring at room temperature pentyl iodide (0.063ml, 0.484mmol) was added and stirring continued under nitrogen at room temperature for 18 hours. The reaction mixture was diluted with water (25ml) and extracted with EtOAc (2x25ml). The combined organic extracts were dried ($MgSO_4$) filtered and evaporated. Purification by SPE (Si, 5g) eluting with 4:1 EtOAc/cyclohexane afforded the title compound as a white solid (96mg, 74%); m/z 297.2[MH^+].

b) 8-chloro-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

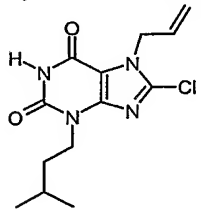


A flask containing tetrakis(triphenylphosphine)-palladium (0) (56mg, 0.049mmol) was flushed with nitrogen, before a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (96mg, 0.323mmol) in anhydrous THF (1.5ml) was added, followed by DMSO (0.1ml) and morpholine (0.28ml, 0.049mmol). The resulting mixture was stirred at room temperature under nitrogen for 72 hours. The reaction mixture was dissolved in EtOAc (25 ml) and washed with 2M HCl aq. (25ml). The organic extract was dried ($MgSO_4$) filtered and evaporated under reduced pressure. Purification by amino propyl SPE (2g) loading and washing with methanol and then eluting the product with 5% acetic acid in methanol. Evaporation of fractions containing product afforded the title compound as a white solid (27mg, 33%). NMR; δ_H (400MHz, d^6-DMSO) 0.85 (t, 3H, J=7Hz), 1.20-1.34 (m, 4H), 1.57-1.67 (m, 2H), 3.84 (t, 2H, J=7Hz), 11.19 (s, 1H), 14.38 (br. s, 1H); m/z 257.2[MH^+].

Example 13: 8-chloro-3-(3-methylbutyl)-3,7-dihydro-1*H*-purine-2,6-dione

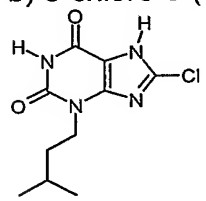


a) 8-chloro-3-(3-methylbutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



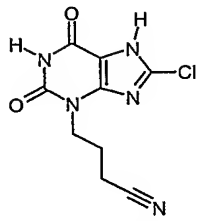
A solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.6mmol) in DMF (40ml) was treated with sodium carbonate (0.9g, 8.5mmol) and 1-bromo-3-methylbutane (1.04g, 6.9mmol). The stirred mixture was heated at 50°C for 18 hours then cooled and evaporated to dryness. The residue was treated with water (60ml) and extracted with ethyl acetate (3x80ml). The organic fractions were combined, dried over magnesium sulfate, filtered and evaporated. The residue was triturated with a mixture of diethyl ether and cyclohexane to reveal the product as a white solid which was filtered off and dried. This gave the title compound as a white solid m/z 297[MH^+].

b) 8-chloro-3-(3-methylbutyl)-3,7-dihydro-1*H*-purine-2,6-dione



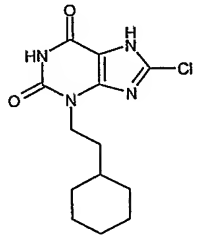
A solution of 8-chloro-3-(3-methylbutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.074g, 0.25mmol) in THF (2ml) was treated with morpholine (0.035ml, 4.0mmol) and the mixture degassed by the repeated alternate application of vacuum and nitrogen to the reaction vessel. The mixture was then treated with a solution of tetrakis(triphenylphosphine)palladium(0) (0.03g, 0.026mmol) in degassed THF (0.5ml). After 2 hours the mixture was treated with 2M aqueous hydrochloric acid (2ml) and diethyl ether (3ml). The precipitated product was filtered off, washed with diethyl ether and dried. This yielded the title compound as a white solid (0.036g, 56%). NMR δ_H (400MHz, d^6-DMSO); 0.91(d, 6H, J=6.3 Hz), 1.47-1.62(m, 3H), 3.87(t, 2H, J=7.5 Hz), 11.19(br. s, 1H), 14.38(br. s, 1H); m/z 257, 259[MH^+].

Example 14: 4-(8-chloro-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile



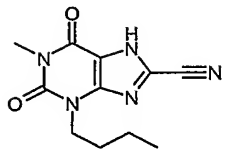
Prepared as example 13 using 4-bromobutyronitrile as alkylating agent
NMR δ_H (400MHz, d^6-DMSO); 1.89-2.00(m, 2H), 2.55(t, 2H, J=7.0Hz), 3.95(t, 2H, J=6.5Hz), 11.25(br. s, 1H), 14.40(br. s, 1H); m/z 254 [MH^+].

Example 15: 8-chloro-3-(2-cyclohexylethyl)-3,7-dihydro-1*H*-purine-2,6-dione

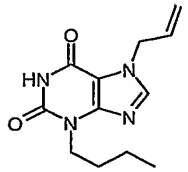


8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.442 mmol) was stirred with sodium carbonate (52mg, 0.486 mmol) in dry DMF (3ml) for 30 min. Cyclohexylethyl bromide (93mg, 0.486 mmol) was added, and the mixture was stirred at 37-40°C under nitrogen for 65h, followed by heating at 90°C for 18h. After cooling, the solution was degassed by evacuating and introducing nitrogen several times, and tetrakis(triphenylphosphine)palladium(0) (76mg, 0.066 mmol) and morpholine (0.385ml, 4.42 mmol) were added and the mixture stirred for 18h. A further quantity of tetrakis(triphenylphosphine)palladium(0) (50mg, 0.043 mmol) and morpholine (0.2ml) were added and stirring continued for a further 1h. Ethyl acetate and 2M aqueous HCl were added (ca. 10ml each) and the organic layer separated, washed with brine and evaporated. The residue was dissolved in THF and loaded onto a 5g aminopropyl SPE cartridge. The cartridge was washed with THF followed by MeOH, and the acidic product eluted with AcOH in MeOH (5% rising to 10%). The product thus obtained was further purified by autoprep HPLC to provide the title compound, 5.5mg, 3%
NMR δ_H (400MHz, d^6-DMSO) 0.80-0.95 (m, 2H), 1.05-1.35 (m, 4H), 1.45-1.55 (m, 2H), 1.55-1.70 (m, 3H), 1.70-1.80 (m,2H), 3.86 (t, 2H, J = 8Hz), 11.07 (s, 1H), one exchangeable not observed. m/z 297 (MH^+),

Example 16: 3-butyl-1-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile

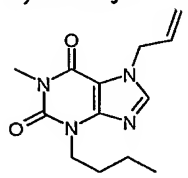


a) 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



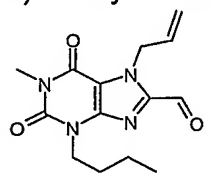
A stirred solution of 7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (10g, 52mmol) in anhydrous DMF (100ml) was treated with K_2CO_3 (7.91g, 57.2mmol) and, after 10 minutes, BuI (6.51ml, 57.2mmol). After reacting for 2 days the reaction mixture was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to give an off-white solid. This was washed with hot cyclohexane and dried under vacuum to give the title compound (8.87g, 68%); m/z 249.3[MH^+].

b) 3-butyl-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



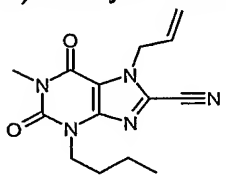
A stirred solution of 3-butyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.0g, 4.03mmol) in anhydrous DMF (10ml) was treated with Na_2CO_3 (470mg, 4.43mmol) followed by Methyliodide (275ul, 4.43mmol). The mixture was heated at 35°C for 17 hours. K_2CO_3 (500mg, 3.6mmol) and Methyliodide (275ul, 4.43mmol) were added and then stirred at 50°C for a further 18 hours. The reaction mixture was allowed to cool then partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated and the aqueous extracted once more with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated giving a yellow/brown oil (1.24g). The product was purified by silica SPE (10g), eluting with EtOAc/cyclohexane mixtures. The product fractions were combined and concentrated to afford the title compound as a pale yellow solid (1.11g, quant.); m/z 263.3[MH^+].

c) 3-butyl-1-methyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehyde



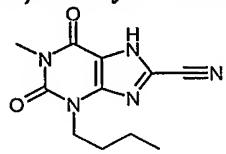
A pre-dried flask was charged with 3-butyl-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (300mg, 1.14mmol) and anhydrous THF (6ml), cooled to –75°C under nitrogen, then treated with LiHMDS (1.37ml of a 1.0M solution in THF). The resulting solution was allowed to warm to –60°C over 1.5 hours before the addition of anhydrous DMF (177ul, 2.29mmol). The solution was allowed to warm to –10°C over 3 hours then it was quenched with sat. NH_4Cl (aq) solution. The mixture was partitioned between 1M HCl (aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated giving a brown oil (350mg). The product was purified by SPE (Si, 10g) eluting with EtOAc/ cyclohexane mixtures to give the title compound as a white solid (131mg, 39%); NMR; δ_H (400MHz, d^6-DMSO) 0.91 (t, 3H, J=7.5Hz), 1.28-1.39 (m, 2H), 1.63-1.73 (m, 2H), 3.25 (s, 3H), 4.02 (t, 2H, J=7.5Hz), 5.03 (dd, 1H, J=17 and 1Hz), 5.17 (dd, 1H, J=10 and 1Hz), 5.31 (app. d, 2H, J=5.5Hz), 5.98-6.09 (m, 1H), 9.88 (s, 1H).

d) 3-butyl-1-methyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile



A solution of 3-butyl-1-methyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehyde in anhydrous pyridine (5ml) was treated with hydroxylamine hydrochloride (63mg, 0.91mmol) and heated at 50°C for 1 hour. The mixture was allowed to cool, concentrated, and treated with acetic anhydride (5ml) then heated at 100°C for 2.5 hours and 125°C for 45 minutes. Again the mixture was allowed to cool then partitioned between water and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound as a yellow residue (230mg crude, 114%); m/z 288.3[MH^+].

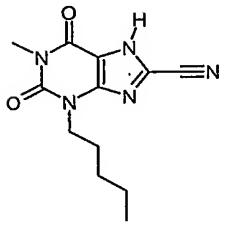
e) 3-butyl-1-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile



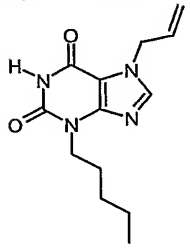
A solution of 3-butyl-1-methyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile (230mg, 0.80mmol) in anhydrous THF (5ml) and anhydrous DMSO (0.5ml) was treated with $Pd(PPh_3)_4$ (185mg, 0.16mmol). The mixture was degassed under gentle vacuum, morpholine (698uL) added, and left to stir at rt under nitrogen for 2 hours. The yellow solution was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up in MeOH and passed down and amino-propyl SPE (5g), eluting with MeOH followed by 5%AcOH then 10%, 20% and 30%AcOH/MeOH mixtures. The product fractions were combined and concentrated to afford a pale yellow solid (116mg). This was washed with MeOH and the title compound a white solid was collected by filtration and dried under

vacuum (55mg, 28%). NMR; δ_H (400MHz, d^6-DMSO) 0.90 (t, 3H, J=7.5Hz), 1.25-1.35 (m, 2H), 1.59-1.68 (m, 2H), 3.24 (s, 3H), 3.96 (t, 2H, J=7Hz), NH not observed to δ_H 15; m/z 248.2[MH^+].

Example 17: 1-Methyl-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile

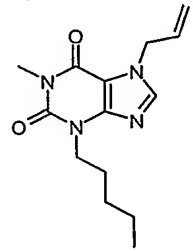


a) 3-Pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



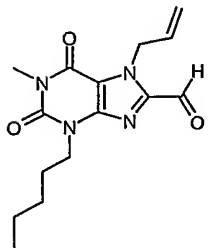
7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.61g, 3.2mmol), sodium carbonate (0.60g, 5.7mmol) and pentyl iodide (0.64g, 3.2mmol) were stirred in DMF (5ml) at 50°C for 18h. The solution was cooled, separated between ethyl acetate and brine and the organics isolated, dried ($MgSO_4$) and concentrated. Chromatography over silica (gradient elution dichloromethane to 5:1 dichloromethane/ethyl acetate) provided the title compound as a pale yellow solid (0.47g, 56%). m/z 263[MH^+]

b) 1-methyl-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



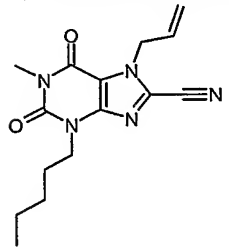
3-Pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.20g, 0.76mmol), potassium carbonate (0.4g, 2.9mmol) and methyl iodide (0.5ml, 4.9mmol) were stirred and heated at 50°C in DMF (5ml) for 3h. The solution was allowed to cool and separated between ethyl acetate and brine. The organics were isolated, dried ($MgSO_4$) and concentrated to provide the title compound (0.21g, 100%). m/z 277[MH^+]

c) 1-Methyl-2,6-dioxo-3-pentyl-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehyde



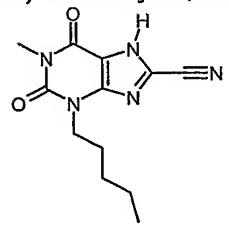
To 1-methyl-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.05g, 3.6mmol) in THF (15ml) at -78°C was added LiHMDS (4ml, 1M in hexane, 4mmol) over 10min and the solution stirred for 0.5h. DMF (0.5ml) was added and the solution stirred at -78°C for a further 0.5h then allowed to warm to ambient temperature with the cooling bath over 2h. The reaction was quenched with 2N hydrochloric acid (3ml) and partioned between ethyl acetate and brine. The organics were isolated, dried and concentrated. The crude product was chomatographed over silica (gradient elution dichloromethane to 5:1 dichloromethane/ethyl acetate) to afford the title compound as a white solid (0.35g, 30%). m/z 305[MH^+]

d) 1-Methyl-2,6-dioxo-3-pentyl-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile



1-Methyl-2,6-dioxo-3-pentyl-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbaldehyde (0.18g, 0.6mmol) and hydroxylamine hydrochloride (0.053g, 0.76mmol) were heated at 50°C in pyridine (5ml) for 1h then cooled to ambient. Acetic anhydride (0.08g, 0.78mmol) was added and the solution stirred for 18h. The solution was concentrated to provide the acetate and dissolved in acetic anhydride (3ml) and heated to 130°C for 3h, cooled and concentrated to yield crude product. Chromatography over silica (eluting with dichloromethane) yielded the title compound as a clear oil (0.17g, 95%). m/z 302[MH^+]

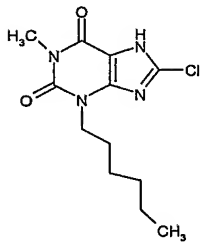
e) 1-Methyl-2,6-dioxo-3-pentyl-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile



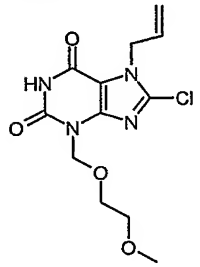
1-Methyl-2,6-dioxo-3-pentyl-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile (0.17g, 0.56mmol) and morpholine (0.6ml, 6.7mmol) were dissolved in THF (5ml) containing DMSO (0.5ml). The flask containing the solution was placed under vacuum and the air replaced with nitrogen (x3). Tetrakis(triphenylphosphine)palladium (0) (0.13g, 0.11mmol) was added and the solution stirred for 2.5h. The solution was separated between ethyl

acetate (20ml) and 2N hydrochloric acid (10ml) and the organics isolated and washed with brine (3x10ml). The organics were then washed with 2N sodium hydroxide solution (2x10ml) and the aqueous acidified with 2N hydrochloric acid and extracted with ethyl acetate (2x10ml). The organics were isolated, dried ($MgSO_4$) and concentrated to yield the title compound (0.026g, 18%). NMR; δ_H (400MHz, $CDCl_3$) 0.92 (t, 3H, J=7Hz), 1.32-1.43 (m, 4H), 1.79 (m, 2H), 3.54 (s, 3H), 4.15 (t, 2H, J=7.5Hz,),14.35 (br. s, 1H); m/z 262[MH^+]

Example 18: 8-chloro-3-hexyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione

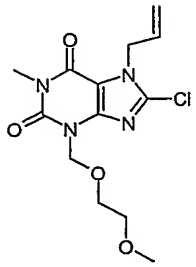


a) 8-chloro-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



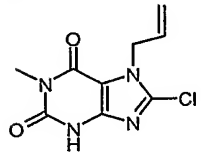
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (6g, 26.5mmol) in anhydrous DMF (30ml) was added sodium carbonate (3.09g, 29.15mmol). After 10 minutes stirring at room temperature methoxyethoxymethylchloride (3.03ml, 26.5mmol) was added and stirring continued under nitrogen at room temperature for 66 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (100ml) and washed with brine (100ml), the aqueous extract was extracted with DCM (100ml) and the organic extracts dried ($MgSO_4$) combined and concentrated *in vacuo*. The residue was triturated with EtOAc and the solid filtered off. Concentration of the filtrate afforded a light brown oil that was absorbed onto silica and purified by SPE (Si, 50g) eluting with a gradient of 1:1 EtOAc/cyclohexane-EtOAc to afford the title compound as a white solid (2g, 24%), m/z 315.2[MH^+].

b) 8-chloro-1-methyl-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2g, 6.37mmol) in anhydrous DMF (15ml) was added sodium carbonate (0.743g, 7mmol). After 10 minutes stirring at room temperature methyliodide (0.44ml, 7mmol) was added and stirring continued under nitrogen at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (100ml) and washed with brine (100ml). The organic extract was dried ($MgSO_4$) filtered and evaporated to afford the title compound as a tan oil (85% pure) (2.98g, quant.), m/z 329.2[MH^+].

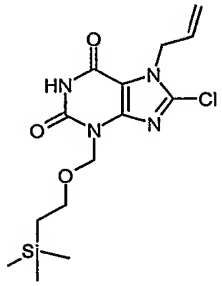
c) 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-1-methyl-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.9g, 6.37mmol) in dioxan (20ml) and water (20ml) was added 5M HCl (20ml). The resulting mixture was heated at 100°C under nitrogen for 18 hours. The reaction mixture was then concentrated *in vacuo*, the residue was dissolved in EtOAc (100ml) and washed with water. The organic extract was dried ($MgSO_4$) filtered and evaporated. Purification by SPE (Si, 20g) eluting 2:3 EtOAc/cyclohexane afforded the title compound as a white solid (1.04g, 68%). m/z 241.1[MH^+].

Alternatively 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione can be prepared with SEM protection.

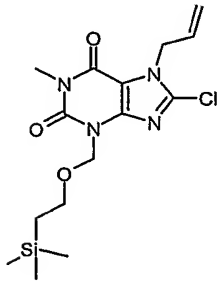
a) 8-chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (5g, 22.1mmol) in DMF (80ml) was added 2-2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and

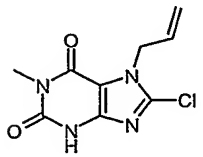
sodium carbonate (2.6g, 24.2mmol). After stirring overnight at room temperature overnight further 2-2-(trimethylsilyl)ethoxymethyl chloride (4.3ml, 24.2mmol) and sodium carbonate (1.3g, 12.1mmol) were added and stirring continued for 2 hours. The reaction mixture was then partitioned between 5% LiCl aq and ethylacetate. The organic extract was separated, washed with brine, dried ($MgSO_4$) and concentrated. Purification by Biotage™ chromatogratphy using a silica cartridge eluting 1:4-1:2 ethyl acetate/cyclohexante afforded the title compound (3.14g, 40%); m/z 374.2[MNH_4^+].

b) 8-chloro-1-methyl-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione



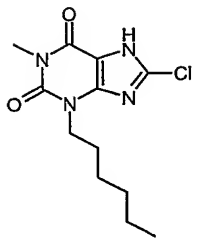
To a solution of 8-chloro-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione (3.14g, 8.82mmol) in DMF (50ml) was added methyl iodide (0.659ml, 10.58mmol) and caesium carbonate (3.45g, 10.58mmol) and the reaction mixture stirred overnight at room temperature. The reaction mixture was partioned between water and ethyl acetate. The organic extract was separated, washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound 2.99g (92%); m/z 388 [MNH_4^+].

c) 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



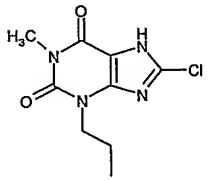
To a solution of 8-chloro-1-methyl-7-(2-propen-1-yl)-3-({[2-(trimethylsilyl)ethyl]oxy}methyl)-3,7-dihydro-1*H*-purine-2,6-dione (2.99g, 8.08mmol) in DCM (20ml) was added TFA (10ml) and the reaction stirred for 2.5 hours at room temperature. The reaction mixture was then concentrated and the residue treated with further DCM and evaporated once more. Purification by SPE (Si) eluting 1:9-4:1 ethylacetate/cyclohexane afforded impure product (1.31g), which was dissolved in methanol (20ml) and treated with sat. potassium carbonate aq. (20ml). After stirring overnight the mixture was partitioned between water containing 2M HCl (1ml) and ethyl acetate. The organic extract was separated, washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound 0.87g (45%); m/z 241.1 [MH^+].

d) 8-chloro-3-hexyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione



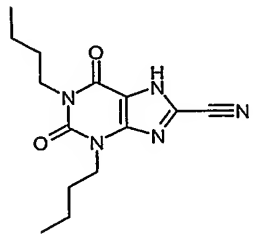
To a solution of 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.42mmol) in anhydrous DMF (3ml) was added sodium carbonate (58mg, 0.54mmol), after 10 minutes stirring hexyl iodide (0.08ml, 0.54mmol) was added and the reaction mixture stirred at room temperature under nitrogen for 90 hours. $Pd(PPh_3)_4$ (73mg, 0.063mmol) was then added and the reaction vessel evacuated and flushed with nitrogen (x3), morpholine (0.37ml, 4.3mmol) was added and stirring at room temperature under nitrogen continued for 4 hours. The reaction mixture was diluted with EtOAc (25ml) and washed with 2M HCl aq.(25ml). The organic extract was dried ($MgSO_4$) filtered and evaporated. Purification by aminopropyl SPE (5g) loading the compound and washing with MeOH before eluting the product with 5% AcOH/MeOH afforded the title compound as a white solid (65mg, 54%). NMR; δ_H (400MHz, d^6-DMSO)) 0.85 (t, 3H, J=7Hz), 1.23-1.33 (m, 6H), 1.58-1.68 (m, 2H), 3.22 (s, 3H), 3.91 (t, 2H, J=7.5Hz), 14.46 (br. s, 1H); m/z 285.3 [MH^+].

Example 19: 8-chloro-1-methyl-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione

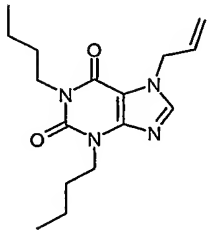


Prepared in similar fashion to Example 18 but using propyl iodide to alkylate on N3.
NMR δ_H (400MHz, d^6-DMSO) 0.87(t, 3H, J=7.5Hz), 1.61-1.73 (m, 2H), 3.22 (s, 3H), 3.89 (t, 2H, J=7.5Hz), 14.45 (br. s, 1H), m/z 243 [MH^+]

Example 20: 1,3-dibutyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile

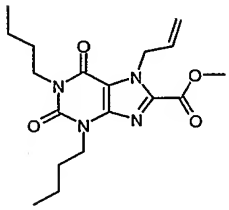


a) 1,3-dibutyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



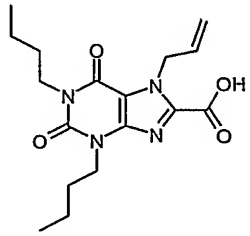
A solution of 1,3-di-N-butyl xanthine (10g, 38mmol) in anhydrous DMF (80ml) was treated with K_2CO_3 (5.2g, 38mmol) followed by allyl bromide (3.6ml, 42mmol). The mixture was heated at 55°C under nitrogen for 18 hours. After cooling to rt the mixture was partitioned between water and EtOAc. A few mls of 2M HCl(aq) was added to aid separation. The organic layer was separated and the aqueous extracted once more with EtOAc. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound as an off-white solid (12.23g, 106%). m/z 305.3[MH^+].

b) Methyl 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carboxylate



A solution of 1,3-dibutyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.0g, 9.9 mmol) in anhydrous THF (30ml) was cooled to –50°C and treated with LiHMDS (18ml of a 1.0M solution in THF, 17.8mmol). After 1 hour at –50°C methyl chloroformate (1.9ml, 24.6mmol) was added and the mixture allowed to warm to –30°C over 2 hours, then quenched with sat. NH_4Cl (aq) solution. The mixture was partitioned between EtOAc and 1M HCl (aq). The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated giving a dark orange oil (4.07g). The oil was taken up in 15% EtOAc/ cyclohexane and passed down a Si Biotage™ chromatography column. The product fractions were combined and concentrated to afford the title compound as a yellow solid (1.35g, 38%). m/z 363.2 [MH^+].

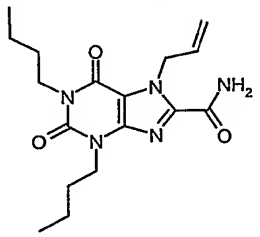
c) 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carboxylic acid



A stirred solution of methyl 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carboxylate (1.30g, 3.6mmol) in MeOH (15ml) was treated with LiOH (215mg) and

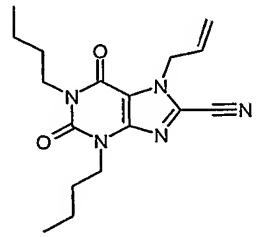
water (1.5ml). After 3 hours at rt the mixture was diluted with water and the pH adjusted to ca. pH5 with 2M HCl(aq). EtOAc was added and then separated, washed with brine, dried ($MgSO_4$) and concentrated to afford the title compound as a yellow solid 85% pure (1.2g, 88%). m/z. 349.2[MH^+].

d) 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carboxamide



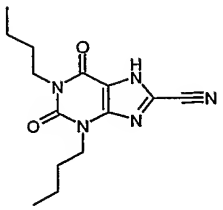
A stirred solution of 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carboxylic acid (1.0g, 2.9mmol) in anhydrous DMF (10ml) was sequentially treated with DIPEA (1.1ml), PyBOP, and 2M NH_3 (3.6ml). After 2 hours the product mixture was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with sat. $NaHCO_3$(aq) solution, brine, then dried ($MgSO_4$) and concentrated giving an orange oil (ca. 2g). The product was purified by Biotage™ chromatography eluting with 5%→40% EtOAc/cyclohexane mixtures. The appropriate fractions were combined and concentrated to give the amide 90% pure (790mg, 78%). m/z. 392.3[M+formic acid-H]$^-$.

e) 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile



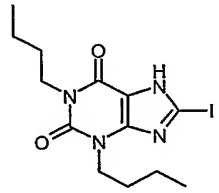
A solution of 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carboxamide (300mg) in anhydrous DMF (7ml) at 0°C was treated dropwise with $POCl_3$ (237uL). The ice-bath was removed and after 2 hours the mixture was partitioned between water and Et_2O. The aqueous layer was re-extracted with Et_2O and the combined extracts separated, washed with water (x2), brine, then dried ($MgSO_4$) and concentrated, giving a yellow oil (312mg). The oil was taken up in cyclohexane and purified by SPE (Si, 10g) eluting with EtOAc/cyclohexane mixtures. Concentration of the product fractions gave the title compound as a colourless oil (150mg, 53%);. m/z. 330.3[MH^+].

f) 1,3-dibutyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile



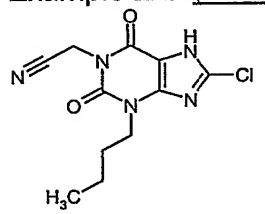
A solution of 1,3-dibutyl-2,6-dioxo-7-(2-propen-1-yl)-2,3,6,7-tetrahydro-1*H*-purine-8-carbonitrile (140mg, 0.43mmol) in anhydrous THF (4ml) and anhydrous DMSO (0.4ml) was treated with $Pd(PPh_3)_4$ (74mg, 0.064mmol). The mixture was degassed under gentle vacuum, morpholine (371uL) added, and left to stir at rt under nitrogen for 4 hours. The yellow solution was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up in MeOH and passed down and amino-propyl SPE (5g), eluting with MeOH followed by 5%→50% AcOH/ MeOH. The product eluted with a small impurity which was washed out, after concentrating, with cyclohexane to afford the title compound as an off-white solid (30mg, 24%).NMR δ_H (400MHz, d^6-DMSO) 0.89 (app. td, 6H, J=7 and 3Hz), 1.25-1.35 (m, 4H), 12.48-1.55 (m, 2H), 1.58-1.69 (m, 2H), 3.87 (t, 2H, J=7Hz), 3.95 (t, 2H, J=7Hz), NH not observed to δ_H 15; m/z 290.3[MH^+].

Example 21: 1,3-dibutyl-8-iodo-3,7-dihydro-1*H*-purine-2,6-dione



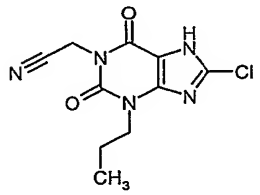
A stirred solution of 1,3-di-N-butyl xanthine (100mg, 3.39mmol) in anhydrous DMF (3ml) was treated with NIS (94mg, 3.75mmol) and left to stir at rt. under nitrogen for 23 hours. The mixture was partitioned between sat. Na_2SO_3(aq) solution and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by passing down an SPE (Si, 5g) cartridge eluting with EtOAc/ cyclohexane mixtures. The product fraction was concentrated to afford the title compound as a white solid (75mg, 51%); NMR; δ_H (400MHz, d^6-DMSO) (app.td, 6H, J=7.5 and 4Hz), 1.21-1.34 (m, 4H), 1.45-1.54 (m, 2H), 1.56-1.66 (m, 2H), 3.84 (t, 2H, J=7.5Hz), 3.93 (t, 2H, J=7.5Hz), 14.10 (s, 1H); m/z 391.3[MH^+].

Example 22: (3-butyl-8-chloro-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile

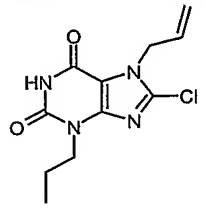


To a mixture of 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.707mmol) and Cs_2CO_3 (254mg, 0.778mmol) in anhydrous DMF (5ml) was added chloroacetonitrile (0.054ml, 0.85mmol). The mixture was heated at 50°C for 18 hours then allowed to cool to rt and degassed under a gentle vacuum then nitrogen introduced. This was repeated twice. $Pd(PPh_3)_4$ (82mg, 0.071mmol) was added and the mixture degassed once more, before morpholine (0.617ml, 7.07mmol) was added and the mixture left to stir for 3 hours at rt. The mixture was partitioned between 2M HCl(aq) and EtOAc. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up in MeOH and passed down an amino-propyl SPE (5g), eluting with MeOH followed by 5-10% AcOH/ MeOH. The product fraction was concentrated giving the title compound 52mg (26%); NMR; δ_H (400MHz, d^6-DMSO) 0.90 (t, 3H, J=7.5Hz), 1.26-1.37 (m, 2H), 1.60-1.69 (m, 2H), 3.94 (t, 2H, J=7.5Hz), 4.87 (s, 2H), 14.72 (br s, 1H); m/z 299.2 [MNH_4^+].

Example 23: (8-chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile

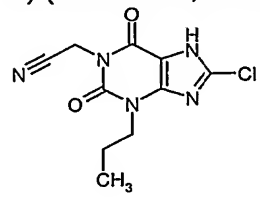


a) 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione



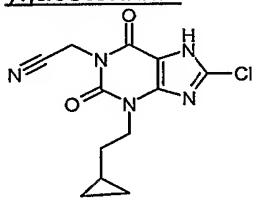
A mixture of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.6mmol), 1-iodopropane (1.2g, 6.9mmol) and sodium carbonate (0.9g, 8.5mmol) in DMF (40ml) was heated at 50°C for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue treated with water (60ml) and extracted with ethyl acetate (3x 80ml). The combined organic extracts were dried ($MgSO_4$) filtered and evaporated. The residue was triturated with ether/cyclohexane, the solid was filtered off and dried to afford the title compound (0.82g, 46%); m/z 269.1 [MH^+].

b) (8-chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile



A solution of 8-chloro-7-(2-propen-1-yl)-3-propyl-3,7-dihydro-1*H*-purine-2,6-dione (0.067g, 0.25mmol) in DMF (2ml) was treated with caesium carbonate (0.082g, 0.25mmol) and bromoacetonitrile (0.044g, 0.37mmol). The mixture was heated at 80°C for 4 hours then cooled to ambient temperature. The DMF was removed *in vacuo* and the residue treated with THF (2ml). The solvent was degassed by the successive application of vacuum and nitrogen pressure to the reaction mixture. The mixture was then treated with morpholine (0.035ml, 0.4mmol) and tetrakis(triphenylphosphine)palladium(0) (0.03g, 0.026mmol). After 2 hours the mixture was treated with 2M aqueous hydrochloric acid (2ml) and the product extracted with chloroform (3x5ml). The organic fractions were combined and evaporated. The residue was subjected to purification by mass-directed HPLC to afford the title compound as a white solid (0.022g, 33%). NMR; δ_H (400MHz, d^6-DMSO), 0.88 (t, 3H, J=7.5Hz), 1.63-1.74 (m, 2H), 3.91 (t, 2H, J=7.5Hz), 4.87 (s, 2H), NH not observed to δ_H 14; m/z 268 [MH^+].

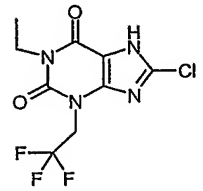
Example 24: [8-chloro-3-(2-cyclopropylethyl)-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-1-yl]acetonitrile



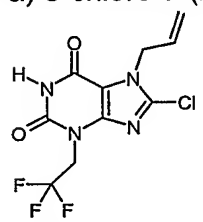
Prepared as (8-chloro-2,6-dioxo-3-propyl-2,3,6,7-tetrahydro-1*H*-purin-1-yl)acetonitrile (example 23) using 8-chloro-3-(2-cyclopropylethyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione.

NMR δ_H (400MHz, d^6-DMSO) -0.06-0.00 (m, 2H), 0.31-0.39 (m, 2H), 0.64-0.74 (m, 1H), 1.57 (q, 2H, J=7Hz), 4.04 (t, 2H, J=7Hz), 4.87 (s, 2H), 14.68 (br. s, 1H); m/z 294 [MH^+].

Example 25: 8-chloro-1-ethyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione



a) 8-chloro-7-(2-propen-1-yl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione



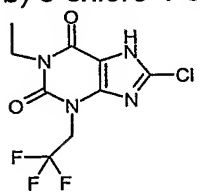
To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (1.5g, 6.62mmol) in anhydrous DMF (50ml) was added sodium bicarbonate (0.98g, 9.25mmol) followed by

1,1,1-trifluoro-2-iodoethane (1.20g, 5.72mmol) and the mixture heated with stirring for 6h at 50°C under an atmosphere of nitrogen. The solution was allowed to cool to ambient temperature for 10h then heated for 48h at 120°C. Additional 1,1,1-trifluoro-2-iodoethane (0.43g, 2.05mmol) was added and the mixture heated to 120°C for a further 3h. The solvent was removed under reduced pressure and the residue triturated with DCM then filtered.

The reaction was repeated using 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.80g, 16.8mmol), sodium bicarbonate (2.45g, 23.1mmol) and 1,1,1-trifluoro-2-iodoethane (4.05g, 19.3mmol) in anhydrous DMF (125ml). The mixture was heated for 16h at 120°C, the solvent removed under reduced pressure and the residue triturated with DCM then filtered.

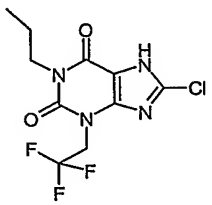
DCM filtrates from the two runs were combined, concentrated under reduced pressure then purified using Biotage™ chromatography (eluting with cyclohexane/ethyl acetate 1:1, then 7:3) to give the title compound as a white solid (1.6g, 23%). m/z 309 [MH^+].

b) 8-chloro-1-ethyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1H-purine-2,6-dione



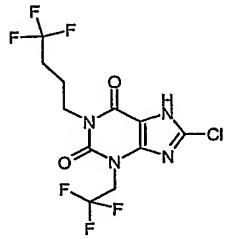
To a solution of 8-chloro-7-(2-propen-1-yl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione (0.070g, 0.23mmol) in anhydrous DMF (2ml) was added caesium carbonate (0.085g, 0.26mmol) followed by 1-iodoethane (0.061g, 0.39mmol). The mixture was heated for 5h at 80°C then stirred for 16h at ambient temperature under an atmosphere of nitrogen. The solvent was removed under reduced pressure using a vacuum centrifuge and the residue dissolved in anhydrous THF (2.5ml). To the mixture was added palladium tetrakis (0.030g, 0.026mmol) and morpholine (0.040g, 0.45mmol) and the reaction mixture degassed using nitrogen then stirred at ambient temperature for 72h. The mixture was partitioned between chloroform and 2N HCl aq., and the aqueous layer re-extracted. Organic extracts were combined and evaporated under a stream of nitrogen then purified using aminopropyl SPE (eluting with acetic acid:methanol:DCM, 1:2:2) to give the title compound as a white solid in >95% purity (0.041g, 60%). NMR δ_H (400MHz, d^4-MeOD) 1.20 (t, 3H, J=7Hz), 4.03 (q, 2H, J=7Hz), 4.73 (q, 2H, J=8.5Hz), m/z 297 [MH^+].

Example 26: 8-chloro-1-propyl-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione



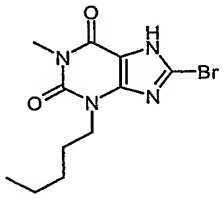
Prepared in similar fashion to Example 25 using propyl iodide to alkylate on N1.
NMR δ_H (400MHz, $CDCl_3$) 0.99 (t, 3H, J=7.5Hz), 1.68-1.79 (m, 2H), 4.07 (t, 2H, J=7.5Hz), 4.77 (q, 2H, J=8.5Hz), NH not observed to δ_H 13; m/z 311 [MH^+].

Example 27:
8-chloro-1-(4,4,4-trifluorobutyl)-3-(2,2,2-trifluoroethyl)-3,7-dihydro-1*H*-purine-2,6-dione

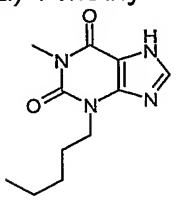


Prepared in similar fashion to Example 25 using 4-bromo-1,1,1-trifluorobutane to alkylate on N1.
NMR ; δ_H (400MHz, d^4-MeOD)1.83-1.95 (m, 2H), 2.14-2.32 (m, 2H), 4.06 (t, 2H, J=7Hz), 4.74 (q, 2H, J=8.5Hz), m/z 377 [M-H]$^-$.

Example 28: 8-Bromo-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

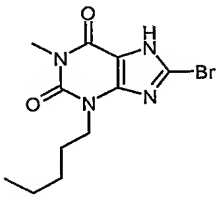


a) 1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



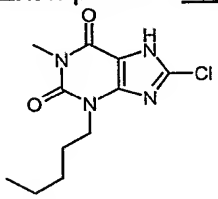
1-methyl-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (0.45g, 1.63mmol), phenylsilane (0.25ml, 2.03mmol) and tetrakis(triphenylphosphine)palladium(0) (0.35g, 0.3mmol) was dissolved in DCM (10ml) containing acetic acid (6ml). The air in the flask was replaced by nitrogen by evacuating the flask then filling with nitrogen (x3) and the reaction mixture heated to 45C for 4h. The solution was allowed to cool diluted with DCM then washed with water then saturated sodium bicarbonate solution. The organics were isolated, dried and concentrated to yield crude product. Purification by SPE (silica) eluting with ether provided the product, 0.06g, 16%. m/z 237 [MH^+].

b) 8-Bromo-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

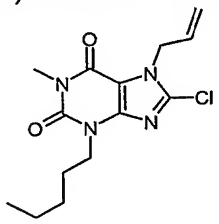


1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione (0.06g, 0.25mmol) was dissolved in DMF (2ml) and N-bromosuccinamide (0.045g, 0.25mmol) added. The mixture was stirred for 18h, concentrated and the crude purified by eluting through an aminopropyl SPE (5g) with first methanol then 5% acetic acid/methanol to elute product. The product was further purified by mass directed auto prep to yield the title compound as a white solid (0.01g, 12%). NMR δ_H (400MHz, d^6-DMSO) 0.86 (t, 3H, J=7Hz), 1.21-1.35 (m, 4H), 1.59-1.68 (m, 2H), 3.22 (s, 3H), 3.91 (t, 2H, J=7.5Hz), 14.39 (br. s, 1H); m/z 315, 317 [MH^+].

Example 29: 8-chloro-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione

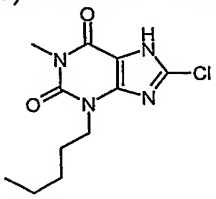


a) 8-chloro-1-methyl-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (3.9g, 13.3mmol) in DMF (35ml) was added cesium carbonate and the mixture stirred for 10min whereupon iodomethane (0.91ml, 14.6mmol) was added and the mixture stirred for 18h. The reaction was partitioned between ethyl acetate and 2N HCl solution and the organics isolated, dried ($MgSO_4$) and concentrated. Chromatography on silica SPE eluting with cyclohexane/ethyl acetate (5%-20%) provided the product as an oil, 2.78g, 68%. m/z 311[MH^+].

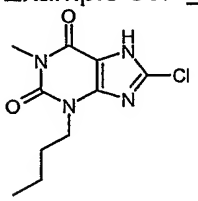
b) 8-chloro-1-methyl-3-pentyl-3,7-dihydro-1*H*-purine-2,6-dione



Tetrakis(triphenylphosphine)palladium (1.0, 0.90mmol) was placed in a flask which was evacuated and then filled with nitrogen (x3). A solution of 8-chloro-1-methyl-3-pentyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.78g, 8.96mmol) in 50ml of THF was added

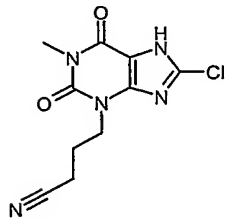
and the flask evacuated once more and nitrogen introduced. DMSO (4.5ml) and morpholine (7.8ml, 89.6mmol) was added and the solution stirred for 5h. The solution was partitioned between ethyl acetate and 2N HCl solution and the organic fraction washed with brine, dried ($MgSO_4$) and concentrated. The crude was purified with an aminopropyl SPE eluting with first methanol then methanol containing 0-15% acetic acid to provide the title compound as a white solid, 1.12g, 46%. NMR δ_H (400MHz, d^6-DMSO) 0.86 (t, 3H, J=7Hz), 1.21-1.35 (m, 4H), 1.59-1.68 (m, 2H), 3.22 (s, 3H), 3.91 (t, 2H, J=7.5Hz), NH not observed; m/z 271 [MH^+].

Example 30: 3-butyl-8-chloro-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione



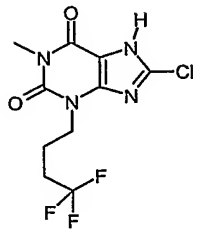
Prepared in similar fashion to Example 29 using 3-butyl-8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione as the starting material.
NMR δ_H (400MHz, d^6-DMSO) 0.88 (t, 3H, J=7Hz), 1.25-1.35 (m, 2H), 1.6-1.66 (m, 2H), 3.22 (s, 3H), 3.91 (t, 2H, J=7.5Hz), 14.46 (br s, 1H); m/z 257 [MH^+].

Example 31:
4-(8-chloro-1-methyl-2,6-dioxo-1,2,6,7-tetrahydro-3*H*-purin-3-yl)butanenitrile



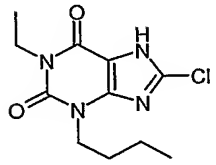
To a mixture of 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (70mg, 0.292mmol) and Na_2CO_3 (37mg, 0.35mmol) in DMF (3ml) was added 4-bromobutyronitrile (0.035ml, 0.35mmol). The mixture was stirred at room temperature overnight, before degassing under a gentle vacuum and introducing nitrogen. $Pd(PPh_3)_4$ (50mg, 0.044mmol) and morpholine (0.254ml, 2.92mmol) was then added sequentially. After two hours stirring at room temperature further fresh $Pd(PPh_3)_4$ (50mg, 0.044mmol) was added and stirring continued overnight. The reaction mixture was partioned between ethyl acetate (20ml) and water (20ml) adding a small amount of 2M HCl to aid separation. The organic layer was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was taken up in MeOH and passed down an amino-propyl SPE (5g), eluting with MeOH followed by 3-5% AcOH/ MeOH. The product fraction was concentrated to afford the title compound 39.7mg (51%); NMR; δ_H (400MHz, d^6-DMSO) 1.91-2.00 (m, 2H), 2.55 (t, 2H, J=7Hz), 3.22 (s, 3H), 4.03 (t, 2H, J=7Hz), 14.49 (br.s, 1H); m/z 268.1 [MH^+].

Example 32: 8-chloro-1-methyl-3-(4,4,4-trifluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione

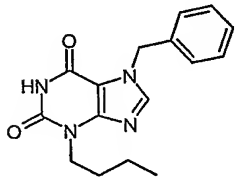


A solution of 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione(0.048g, 0.2mmol) in THF (1ml) was treated with caesium carbonate (0.78g, 0.24mmol) and 4-bromo-1,1,1-trifluorobutane (0.044g, 0.25mmol). The mixture was stirred at ambient temperature for 1 hour then heated at 50°C for 4 hours and then cooled. The mixture was degassed by alternately applying vacuum and nitrogen pressure to the mixture and then treated with morpholine (0.17ml, 2mmol) and tetrakis(triphenylphosphine)palladium(0) (0.023g, 0.02mmol). After 2 hours the mixture was treated cautiously with 2M aqueous hydrochloric acid (2ml) and the product extracted with chloroform (2x4ml). The combined organics were evaporated and the product purified by reverse-phase mass directed HPLC to afford the title compound 6.2mg (10%); NMR; δ_H (400MHz, d^6-DMSO); 1.84-1.92 (m, 2H), 2.28-2.35 (m, 2H), 3.22 (s, 3H), 3.99-4.03 (m, 2H) 14.31 (br.s, 1H); m/z 311.2[MH^+].

Example 33: 3-butyl-8-chloro-1-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



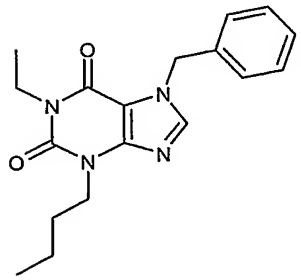
a) 3-butyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione



7-benzyl-3,7-dihydro-1H-purine-2,6-dione (17.14 g, 70.8mmol) [Synthetic Communications, 20(16), *2459-2467*, 1990] and potassium carbonate (11.43 g, 82.8 mmol) were suspended in DMF (400 mL) at 40 °C. After stirring for thirty minutes, butyl iodide (8.76 mL, 77.0 mmol) was added, and the mixture was stirred at 40 °C overnight. 50% Aqueous acetic acid (60 mL) was added, and the solution was concentrated under reduced pressure. The residue was suspended in water (500 mL), and the products were extracted into chloroform. The organics were collected, concentrated, and product was isolated using flash chromatography

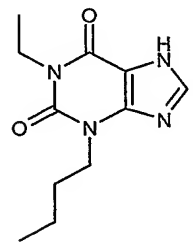
eluting with 1% methanol in dichloromethane to provide the product (9.49 g, 45%); ^{1}H NMR (400MHz; $CDCl_3$) δ: 0.95 (3H, t), 1.34-1.41 (2H, m), 1.70-1.78 (2H, m), 4.05 (2H, t), 5.46 (2H, s), 7.31-7.40 (5H, m), 7.56 (1H, s), 8.21 (1H, br.s); m/z 299[MH^+].

b) 3-butyl-1-ethyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione



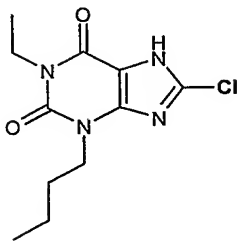
3-butyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione (0.429 g, 1.24 mmol) and potassium carbonate (0.256 g, 1.85 mmol) were suspended in DMF (8 mL), iodoethane (0.113 mL, 1.42 mmol) was added. The reaction mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated to dryness and the residue was partitioned between water and ethyl acetate. The organic layer was washed with water, followed by brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure to yield the title compound; ^{1}H NMR (400MHz; $CDCl_3$) δ: 0.96 (3H, t), 1.25 (3H, t), 1.36-1.45 (2H, m), 1.72-1.76 (2H, m), 4.05-4.13 (4H, m), 5.50 (2H, s), 7.32-7.40 (5H, m), 7.52 (1H, s); m/z 327[MH^+].

c) 3-Butyl-1-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



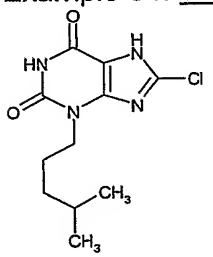
3-butyl-1-ethyl-7-(phenylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione (0.353 g, 1.08 mmol) was dissolved in acetic acid (30 mL), 20% palladium hydroxide on carbon (0.238 g) was added, and the mixture was shaken under hydrogen (at 50 psi) overnight. The catalyst was removed by filtration through Celite® and washed with acetic acid. The filtrate was concentrated under reduced pressure to yield the title compound (0.227g, 89%); ^{1}H NMR (400MHz; $CDCl_3$) δ: 0.97 (3H, t), 1.28 (3H, t), 1.38-1.47 (2H, m), 1.74-1.82 (2H, m), 4.12-4.17 (4H, m), 7.80 (1H, s); m/z 237[MH^+].

d) 3-Butyl-8-chloro-1-ethyl-3,7-dihydro-1*H*-purine-2,6-dione



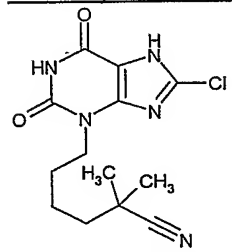
3-Butyl-1-ethyl-3,7-dihydro-1*H*-purine-2,6-dione (100 mg, 0.42 mmol) and NCS (56 mg, 0.42 mmol) were suspended in MeCN (5 mL) and heated at 120°C under microwave irradiation. The reaction mixture was concentrated under reduced pressure and the title compound isolated using HPLC. [HPLC conditions used for the purification : 23 minute run time. Solvents: 0.1% TFA in MeCN and 0.1% TFA in water. MeCN increased from 5% to 95% linearly over 15 minutes. Held at 95% for 2 min. Then decreased to 5% linearly over 1 min., equilibrated at 5% for 5 minutes before next injection.]; ^{1}H NMR (400MHz; $CDCl_3$) δ: 0.97 (3H, t), 1.31 (3H, t), 1.38-1.45 (2H, m), 1.72-1.80 (2H, m), 4.09-4.20 (4H, m), 13.40 (1H, br.s); m/z 271[MH^+].

Example 34: 8-Chloro-3-(4-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione



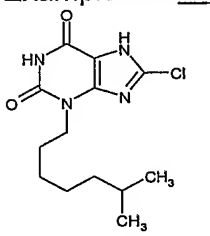
From 1-bromo-4-methylpentane (81mg)
Recrystallised from MeOH
Yield 34.8mg (29%), NMR; (400MHz, d^6-DMSO) δ_H 0.83 (d, 6H, J=8Hz), 1.12-1.22 (m, 2H), 1.55 (septet, 1H, J=8Hz), 1.58-1.68 (m, 2H), 3.83 (t, 2H, J=7.5Hz), 11.20 (s, 1H); m/z 271 [MH^+]

Example 35: 6-(8-Chloro-2,6-dioxo-1,2,6,7-tetrahydro-3H-purin-3-yl)-2,2-dimethylhexanenitrile



From 6-bromo-2,2-dimethylhexanenitrile (100mg)
Recrystallised from MeOH.
Yield 48.5mg (35%); NMR; (400MHz, d^6-DMSO) δ_H 1.27 (s, 6H), 1.35-1.44 (m, 2H), 1.54-1.59 (m, 2H), 1.63-1.72 (m, 2H), 3.88 (t, 2H, J=7Hz), 11.24 (s, 1H); m/z 310 [MH^+]

Example 36: 8-chloro-3-(6-methylheptyl)-3,7-dihydro-1*H*-purine-2,6-dione

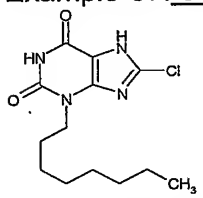


From 1-bromo-6-methylheptane (95mg)

Recrystallised from MeOH.

Yield 36mg (27%), NMR; (400MHz, d^6-DMSO) δ_H 0.83 (d, 6H, J=7.5Hz), 1.10-1.17 (m, 2H), 1.20-1.34 (m, 4H), 1.48 (septet, 1H, J=7.5Hz), 1.58-1.68 (m, 2H), 3.84 (t, 2H, J=8Hz), 11.22 (s, 1H); m/z 299 [MH^+]

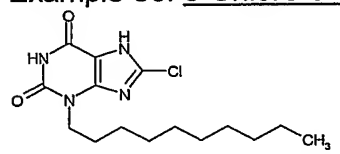
Example 37: 8-Chloro-3-octyl-3,7-dihydro-1H-purine-2,6-dione



8-Chloro-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.44mmol) was stirred with sodium carbonate (52mg, 0.49mmol) in dry DMF (3ml) for 20 min., then 1-iodooctane (118mg, 0.49mmol) was added and the mixture was stirred under nitrogen at 40 C for 65h. After cooling to room temperature, the mixture was thoroughly degassed by evacuating the vessel and refilling with nitrogen several times. Tetrakis(triphenylphosphine)palladium(0) (102mg, 0.09mmol) was added, the mixture degassed again and then morpholine (0.385ml, 4.4mmol) added and stirring continued for 6.5h. 2M HCl and EtOAc were added, and the 2-phase system was filtered. The product was present predominantly in the filtered solid, which was recrystallised from THF-acetonitrile, followed by MeOH, with filtration, to afford the pure title compound.

Yield 48mg (36%); NMR; (400MHz, d^6-DMSO) δ_H 0.84 (t, 3H, J=7Hz), 1.18-1.30 (m, 10H), 1.57-1.66 (m, 2H), 3.84 (t, 2H, J=7.5Hz), 11.22 (s, 1H); m/z 299 [MH^+]

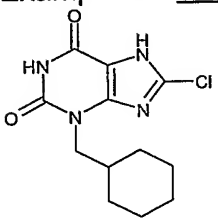
Example 38: 8-Chloro-3-decyl-3,7-dihydro-1H-purine-2,6-dione



Prepared by the method of Example 37, starting from 1-bromodecane (108mg). Further purification was achieved by recrystallisation from MeOH followed by mass-directed autoprep.

Yield 2mg (1.4%); NMR; (400MHz, d^4-methanol) δ_H 0.89 (t, 3H, J=7Hz), 1.26-1.38 (m, 14H), 1.68-1.76 (m, 2H), 3.97 (t, 2H, J=7.5Hz); m/z 327 [MH^+].

Example 39: 8-Chloro-3-(cyclohexylmethyl)-3,7-dihydro-1H-purine-2,6-dione

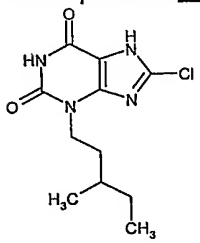


Prepared in a similar manner to Example 37, from (bromomethyl)cyclohexane (87mg) except that an additional heating period at 80 C for 18h was performed.
Recrystallised from MeOH.
Yield 31mg (25%); NMR; (400MHz, d^6-DMSO) δ_H 0.90-1.02 (m, 2H), 1.08-1.20 (m, 3H), 1.53-1.69 (m, 5H), 1.77-1.87 (m, 1H), 3.70 (d, 2H, J=7.5Hz), 11.21 (s, 1H); m/z 283 [MH^+]

General Method for Examples 40-46:

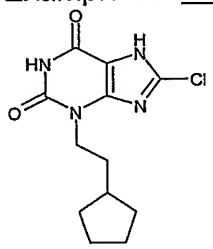
To 8-chloro-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.442mmol) in dry THF (3ml) was added the alcohol (0.442mmol). The mixture was stirred at 0 C as a solution of dibenzyl azodicarboxylate (280mg of 94% purity, 0.88mmol) in dry THF (2ml) was added, followed by a solution of triphenylphosphine (232mg, 0.88mmol) in dry THF, added portionwise over 5 min. After a further 30 min at 0 C, stirring was continued at room temperature for 18h. The mixture was thoroughly degassed by evacuating and refilling the vessel with nitrogen several times, then tetrakis(triphenylphosphine)palladium(0) (102mg, 0.088mmol) was added followed by morpholine (0.385ml, 4.42mmol) and stirring was continued for 4.5h. EtOAc and 2M HCl were added, and the mixture filtered to remove a yellow precipitated solid. The filtrate was separated and the organic phase concentrated and redissolved in a mixture of THF and MeOH. This solution was passed down an aminopropyl SPE, eluting with THF-MeOH (1:1) followed by MeOH and then 5% AcOH in DCM-MeOH (1:1). The product fractions thus obtained were concentrated and recrystallised from MeOH to afford the pure title compound.

Example 40: (+/-)-8-Chloro-3-(3-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione



From (+/-)-3-methyl-1-pentanol 45mg
Yield 20.2mg (17%); NMR; (400MHz, d^6-DMSO) δ_H 0.83 (t, 3H, J=7.5Hz), 0.90 (d, 3H, J=6.5Hz), 1.12-1.21 (m, 1H), 1.30-1.48 (m, 3H), 1.58-1.68 (m, 1H), 3.87 (t, 2H, J=7.5Hz), 11.21 (s, 1H); m/z 271 [MH^+].

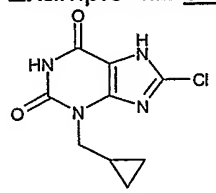
Example 41: 8-Chloro-3-(2-cyclopentylethyl)-3,7-dihydro-1H-purine-2,6-dione



From 2-cyclopentylethanol 50mg

Yield 24.6mg (20%); NMR; (400MHz, d^6-DMSO) δ_H 1.04-1.15 (m, 2H), 1.40-1.67 (m, 6H), 1.70-1.82 (m, 3H), 3.86 (t, 2H, J=7.5Hz), 11.22 (s, 1H); m/z 283 [MH^+]

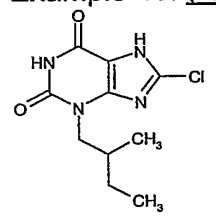
Example 42: 8-Chloro-3-(cyclopropylmethyl)-3,7-dihydro-1H-purine-2,6-dione



From cyclopropylmethanol 32mg

Yield 22.3mg (21%); NMR; (400MHz, d^6-DMSO) δ_H 0.34-0.40 (m, 2H), 0.40-0.48 (m, 2H), 1.17-1.27 (m, 1H), 3.74 (d, 2H, J=7.5Hz), 11.23 (s, 1H); m/z 241 [MH^+].

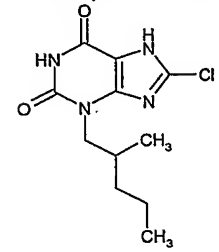
Example 43: (+/-)-8-Chloro-3-(2-methylbutyl)-3,7-dihydro-1H-purine-2,6-dione



From (+/-)-2-methyl-1-butanol 39mg

Yield 12mg (9.5%); NMR; (400MHz, d^6-DMSO) δ_H 0.81 (d, 3H, J=7Hz), 0.86 (t, 3H, J=7.5Hz), 1.06-1.17 (m, 1H), 1.30-1.41 (m, 1H), 1.90-2.00 (m, 1H), 3.68 (dd, 1H, J=13.5 and 8Hz), 3.75 (dd, 1H, J=13.5 and 7.5Hz), 11.22 (s, 1H); m/z 257 [MH^+]

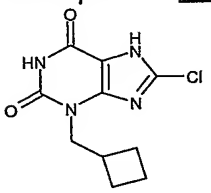
Example 44: (+/-)-8-Chloro-3-(2-methylpentyl)-3,7-dihydro-1H-purine-2,6-dione



From (+/-)-2-methyl-1-pentanol 45mg

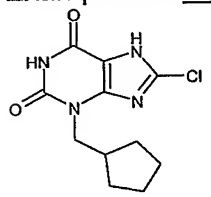
Yield 22.4mg (19%); NMR; (400MHz, d^6-DMSO) δ_H 0.81 (d, 3H, J=7Hz), 0.84 (t, 3H, J=7.5Hz), 1.05-1.16 (m, 1H), 1.16-1.43 (m, 3H), 1.98-2.09 (m, 1H), 3.67 (dd, 1H, J=13.5 and 8Hz), 3.74 (dd, 1H, J=13.5 and 7Hz), 11.22 (s, 1H); m/z 271 [MH^+]

Example 45: 8-Chloro-3-(cyclobutylmethyl)-3,7-dihydro-1H-purine-2,6-dione



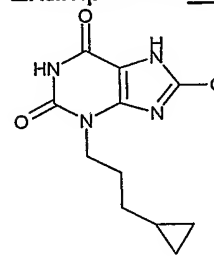
From cyclobutylmethanol 38mg
Yield 30.5mg (27%); NMR; (400MHz, d^6-DMSO) δ_H 1.73-1.85 (m, 4H), 1.86-1.97 (m, 2H), 2.66-2.79 (m, 1H), 3.90 (d, 2H, J=7.5Hz), 11.22 (s, 1H); m/z 255 [MH^+]

Example 46: 8-chloro-3-(cyclopentylmethyl)-3,7-dihydro-1*H*-purine-2,6-dione



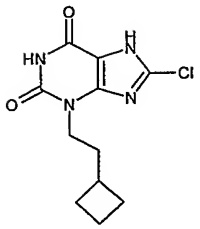
From cyclopentylmethanol 44mg
Yield 15mg (13%); NMR; (400MHz, d^6-DMSO) δ_H 1.20-1.32 (m, 2H), 1.42-1.54 (m, 2H), 1.54-1.66 (m, 4H), 2.32-2.45 (m, 1H), 3.79 (d, 2H, J=8Hz), 11.22 (s, 1H); m/z 269 [MH^+]

Example 47: 8-chloro-3-(3-cyclopropylpropyl)-3,7-dihydro-1H-purine-2,6-dione



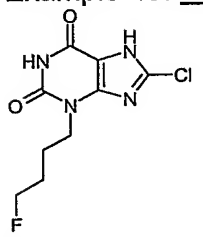
From 3-cyclopropyl-1-propanol (P.J. Wagner, J. Amer. Chem. Soc., 1981, *103*, 3837-3841) (44mg).
Yield 27.7mg (23%); NMR; (400MHz, d^6-DMSO) δ_H -0.03-+0.03 (m, 2H), 0.34-0.40 (m, 2H), 0.65-0.75 (m, 1H), 1.15-1.23 (m, 2H),1.66-1.76 (m, 2H), 3.87 (t, 2H, J=7Hz), 11.15 (s, 1H); m/z 269 [MH^+]

Example 48: 8-chloro-3-(2-cyclobutylethyl)-3,7-dihydro-1H-purine-2,6-dione

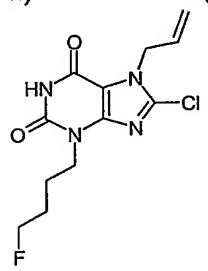


From 2-cyclobutylethanol (P. Vergnon, Eur. J. Med. Chem., 1975, *10*, 65-71) (44mg). Yield 21.5mg (18%); NMR; (400MHz, d^6-DMSO) δ_H 1.53-1.64 (m, 2H), 1.68-1.85 (m, 4H), 1.93-2.03 (m, 2H), 2.19-2.30 (m, 1H), 3.78 (t, 2H, J=7Hz), 11.20 (s, 1H); m/z 269 [MH^+]

Example 49: 8-chloro-3-(4-fluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione



a) 8-chloro-3-(4-fluorobutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (200mg, 0.88mmol, 1eq) in anhydrous DMSO (1ml) in a 1.5ml microwave vial equipped with a stirrer was added sodium bicarbonate (113mg, 1.07mmol, 1.2eq) followed by 1-bromo-4-fluorobutane (114ul, 165mg, 1.06mmol, 1.2eq). The vial was sealed and heated with stirring using a microwave, maintaining the temperature at 120°C for 25min with a maximum power output of 300W. The resulting dark brown solution was diluted with methanol (1ml) and purified by mass directed autopreparative HPLC to give the title compound as a white solid (159mg, 60%). m/z 301.3[MH^+]

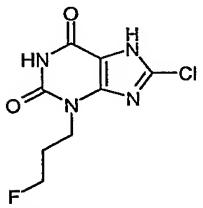
8-chloro-3-(4-fluorobutyl)-3,7-dihydro-1*H*-purine-2,6-dione

To a suspension of 8-chloro-3-(4-fluorobutyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.33mmol, 1eq) in anhydrous DCM (2ml) was added palladium tetrakis (38mg, 0.033mmol, 10% bw), followed by acetic acid (115ul, 121mg, 2.01mmol, 6eq) and phenyl silane (410ul, 360mg, 3.33mmol, 10eq). The resulting light yellow solution was stirred at ambient temperature for 16h to give a dark purple solution. The solvent was removed under a stream of nitrogen and the residue dissolved in a DMSO/methanol solution (3ml, 2:1) with heating. The gelatinous mixture was allowed to cool to ambient temperature,

filtered then purified by mass directed autopreparative HPLC to give the title compound as a white solid (35mg, 43%). m/z 261.2[MH^+] NMR (400MHz, MeOD), δ_H 4.45 (2H, dt, J = 47 and 6Hz), 4.03 (2H, t, J = 7Hz), 1.90 – 1.65 (4H, m).

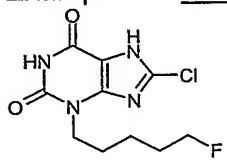
The following compounds were prepared in similar fashion and purified by preparative or mass directed autopreparative HPLC as appropriate:

Example 50: 8-chloro-3-(3-fluoropropyl)-3,7-dihydro-1*H*-purine-2,6-dione



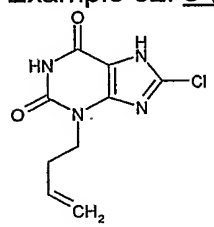
NMR (400MHz, MeOD), δ_H 4.51 (2H, dt, J = 47 and 6Hz), 4.11 (2H, t, J = 7Hz), 2.18 - 2.03 (2H, m). m/z 247 [MH^+]

Example 51: 8-chloro-3-(5-fluoropentyl)-3,7-dihydro-1*H*-purine-2,6-dione



NMR (400MHz, MeOD), δ_H 4.41 (2H, dt, J = 48 and 6Hz), 3.99 (2H, t, J = 8Hz), 1.84 – 1.63 (4H, m), 1.52 – 1.40 (2H, m). m/z 273.29 [MH^-]

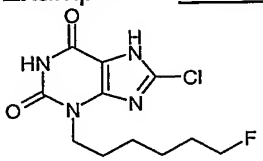
Example 52: 3-(3-buten-1-yl)-8-chloro-3,7-dihydro-1H-purine-2,6-dione



8-chloro-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.44mmol) was stirred with sodium carbonate (52mg, 0.49mmol) in dry DMF (3ml) for 45 min., then 4-bromo-1-butene (66mg, 0.49mmol) was added and the mixture was stirred under nitrogen at 40 C for 65h. After cooling to room temperature, the mixture was thoroughly degassed by evacuating the vessel and refilling with nitrogen several times. Tetrakis(triphenylphosphine)palladium(0) (102mg, 0.09mmol) was added, the mixture degassed again and then morpholine (0.385ml, 4.4mmol) added and stirring continued for 6.5h. 2M HCl and EtOAc were added, and the 2-phase system was filtered to remove a yellow precipitated solid. The organic phase of the filtrate was separated and evaporated. The residue was dissolved with warming in THF-MeOH (1:1) and loaded onto an aminopropyl SPE (5g) which was eluted with THF-MeOH (1:1)

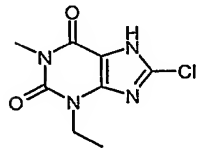
followed by MeOH and then 5% AcOH in MeOH-DCM (1:1). The product fraction was further purified by mass-directed autoprep to afford the title compound.
Yield 27.5mg (26%), NMR; (400MHz, d^6-DMSO) δ_H 2.40 (dt, 2H, J = 7 and 6Hz), 3.93 (t, 2H, J=7Hz), 4.97-5.07 (m, 2H), 5.74-5.85 (m, 1H). 11.22 (s, 1H); m/z 241 [MH^+]

Example 53: 8-chloro-3-(6-fluorohexyl)-3,7-dihydro-1*H*-purine-2,6-dione

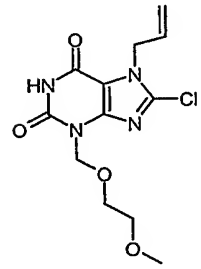


NMR (400MHz, MeOD), δ_H 4.40 (2H, dt, 48 and 6Hz), 3.98 (2H, t, 8Hz), 1.80 – 1.60 (4H, m), 1.52 – 1.35 (4H, m). m/z 287 [MH^+]

Example 54: 8-chloro-3-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione



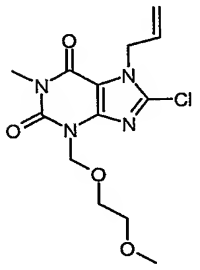
a) 8-chloro-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (6g, 26.5mmol) in anhydrous DMF (30ml) was added sodium carbonate (3.09g, 29.15mmol). After 10 minutes stirring at room temperature methoxyethoxymethylchloride (3.03ml, 26.5mmol) was added and stirring continued under nitrogen at room temperature for 66 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (100ml) and washed with brine (100ml), the aqueous extract was extracted with DCM (100ml) and the organic extracts dried ($MgSO_4$) combined and concentrated *in vacuo*. The residue was trituated with EtOAc and the solid filtered off. Concentration of the filtrate afforded a light brown oil that was absorbed onto silica and purified by SPE (Si, 50g) eluting with a gradient of 1:1

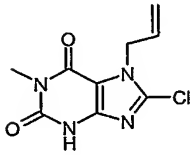
EtOAc/cyclohexane-EtOAc to afford the title compound as a white solid (2g, 24%), m/z 315.2[MH^+]

b) 8-chloro-1-methyl-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



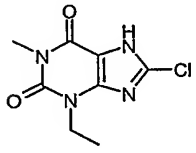
To a solution of 8-chloro-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2g, 6.37mmol) in anhydrous DMF (15ml) was added sodium carbonate (0.743g, 7mmol). After 10 minutes stirring at room temperature methyliodide (0.44ml, 7mmol) was added and stirring continued under nitrogen at room temperature for 18 hours. The reaction mixture was concentrated *in vacuo* and the residue dissolved in EtOAc (100ml) and washed with brine (100ml). The organic extract was dried ($MgSO_4$) filtered and evaporated to afford the title compound as a tan oil (85% pure) (2.98g, quant.), m/z 329.2[MH^+]

c) 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione



To a solution of 8-chloro-1-methyl-3-({[2-(methyloxy)ethyl]oxy}methyl)-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (2.9g, 6.37mmol) in dioxan (20ml) and water (20ml) was added 5M HCl aq. (20ml). The resulting mixture was heated at 100°C under nitrogen for 18 hours. The reaction mixture was then concentrated *in vacuo*, the residue was dissolved in EtOAc (100ml) and washed with water. The organic extract was dried ($MgSO_4$) filtered and evaporated. Purification by SPE (Si, 20g) eluting 2:3 EtOAc/cyclohexane afforded the title compound as a white solid (1.04g, 68%). m/z 241.1[MH^+].

d) 8-chloro-3-ethyl-1-methyl-3,7-dihydro-1*H*-purine-2,6-dione

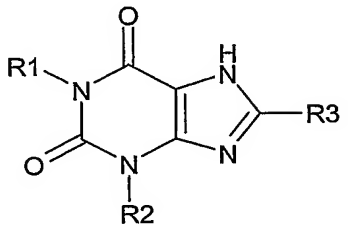


To a solution of 8-chloro-1-methyl-7-(2-propen-1-yl)-3,7-dihydro-1*H*-purine-2,6-dione (100mg, 0.42mmol) in anhydrous DMF (3ml) was added sodium carbonate (58mg, 0.54mmol), after 10 minutes stirring ethyl iodide (0.043ml, 0.54mmol) was added and the reaction mixture stirred at room temperature under nitrogen for 90 hours. $Pd(PPh_3)_4$ (73mg, 0.063mmol) was then added and the reaction vessel evacuated and flushed with nitrogen (x3), morpholine (0.37ml, 4.3mmol) was added and stirring at room temperature under nitrogen continued for 4 hours. The reaction mixtue was diluted with EtOAc (25ml) and washed with 2M HCl aq.(25ml). The organic extract was dried ($MgSO_4$) filtered and evaporated. Purification by aminopropyl SPE (5g) loading the compound and washing with MeOH before eluting the product with 5% AcOH/MeOH afforded the title compound as a white solid (67mg, 70%). NMR; d_H (400MHz, d^6-DMSO) 1.20 (t, 3H, J=7Hz), 3.22 (s, 3H), 3.97(q, 2H, J=7Hz), 14.46 (1H, br s); m/z 227.2$[M-H]^-$.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

Claims

1. An entity selected from: a compound of Formula (I)



(I)

and a physiologically functional derivative thereof, wherein

R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3;
R^2 is selected from: C_{3-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl;
and R^3 is selected from halogen and CN;
with the proviso that:
(i) when R^3 represents Cl, and R^1 represents ethyl, R^2 is other than propyl;
(ii) when R^3 represents Br, and R^1 represents propyl, R^2 is other than propyl;
(iii) when R^3 represents Cl or Br, and R^1 represents butyl, R^2 is other than butyl; and
(iv) when R^1 represents C_{1-4} alkyl, CH_2CN, or $(CH_2)_3CF_3$, R^2 is other than branched alkyl.

2. A compound according to claim 1 wherein
R^1 is selected from: hydrogen, C_{1-4} alkyl, CH_2CN and $(CH_2)_3CF_3$;
R^2 is selected from: C_{3-10} unsubstituted alkyl, $(CH_2)_{1-5}CN$, C_{2-5} alkyl with one or more fluorine substitutions, C_5 alkenyl and C_{1-4} alkyl substituted with cycloalkyl;
and R^3 is selected from halogen and CN;
with the proviso that:
(i) when R^3 represents Cl, and R^1 represents ethyl, R^2 is other than propyl;
(ii) when R^3 represents Cl or Br and R^1 represents butyl, R^2 is other than butyl; and
(iii) when R^1 represents C_{1-4} alkyl, CH_2CN, or $(CH_2)_3CF_3$, R^2 is other than branched alkyl.

3. A compound according to claim 1 or 2 wherein R^1 is selected from: hydrogen and methyl.

4. A compound according to any preceding claim wherein R^2 is selected from: C_{4-6} unsubstituted n-alkyl, $(CH_2)_{1-3}CN$, C_{3-4} alkyl with one or more fluorine substitutions and C_5 alkenyl.

5. A compound according to any preceding claim wherein R^3 represents halogen.

6. A compound according to any preceding claim wherein R^3 is selected from: chlorine and bromine.

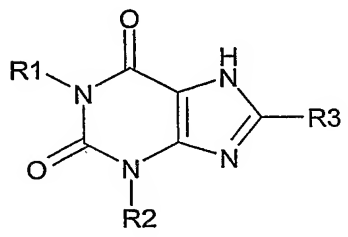
7. A compound according to any preceding claim wherein R^3 represents chlorine.

8. A compound according to any preceding claim for use in human or veterinary medicine.

9. A compound according to any one of claims 1-7, for use in the treatment of disorders of lipid metabolism including dyslipidaemia and hyperlipoproteinaemia and/or of inflammatory diseases or conditions.

10. A compound according to any one of claims 1-7 for use in the treatment of diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure, peripheral vascular disease or stroke.

11. An entity selected from: a compound of Formula (II)



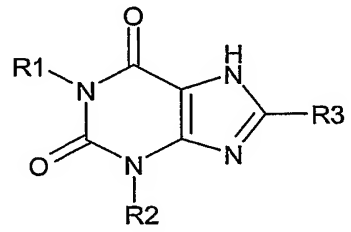
(II)

and a physiologically functional derivative thereof, wherein

R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3;

R^2 is selected from: C_{2-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl;
and R^3 is selected from halogen and CN;
for use in the manufacture of a medicament for treating diabetic dyslipidaemia, mixed dyslipidaemia, heart failure, hypercholesteraemia, cardiovascular disease including atherosclerosis, arteriosclerosis, and hypertriglyceridaemia, type II diabetes mellitus, type I diabetes, insulin resistance, hyperlipidaemia, anorexia nervosa, obesity, coronary artery disease, thrombosis, angina, chronic renal failure or stroke.

12. A method for the treatment of a human or animal subject having a condition where under-activation of the HM74A receptor contributes to the condition or where activation of the receptor will be beneficial, which method comprises administering to said human or animal subject an effective amount of an entity selected from: a compound of Formula (II)



(II)

and a physiologically functional derivative thereof, wherein

R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3;
R^2 is selected from: C_{2-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl;
and R^3 is selected from halogen and CN;

13. A method according to claim 12 wherein the human or animal subject has a disorder of lipid metabolism including dyslipidaemia or hyperlipoproteinaemia or an inflammatory disease or condition.

14. A pharmaceutical formulation comprising a compound according to any one of claims 1-7 and one or more physiologically acceptable diluents, excipients or carriers.

15. A combination for administration together or separately, sequentially or simultaneously in separate or combined pharmaceutical formulations, said combination comprising a compound according to any one of claims 1-7 together with another therapeutically active agent.

16. A pharmaceutical formulation comprising:
    (i) a compound according to any one of claims 1-7;
    (ii) one or more active ingredients selected from statins, fibrates, bile-acid binding resins and nicotinic acid; and
    (iii) one or more physiologically acceptable diluents, excipients or carriers.

17. A method for the preparation of a compound according to any one of claims 1-7 in which R^3 is halogen, the method comprising:
    (i) alkylation at N1 or N3, or dialkylation at N1 and N3 of an N7 protected xanthine;
    (ii) halogenation at C8; and
    (iii) de-protection;

in any order providing de-protection is carried out after alkylation.

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International Bureau

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PCT

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

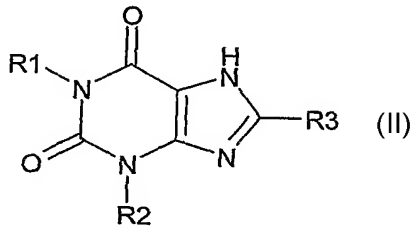
Declarations under Rule 4.17:
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:
— *with international search report*

(88) Date of publication of the international search report:
19 April 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MEDICAMENTS WITH HM74A RECEPTOR ACTIVITY



(II)

(57) Abstract: The present invention provides therapeutically active compounds which are xanthine derivatives, processes for the manufacture of said derivatives, pharmaceutical formulations containing the active compounds and the use of the compounds in therapy, particularly in the treatment of diseases where under-activation of the HM74A receptor contributes to the disease or where activation of the receptor will be beneficial, having the formula (II): wherein R^1 is selected from: hydrogen and C_{1-4} alkyl which may be optionally substituted with one or more groups selected from CN and CF_3, R^2 is selected from: C_{2-10} unsubstituted alkyl, C_{1-10} alkyl substituted with one or more groups selected from fluorine and CN, C_5 alkenyl, unbranched C_4 alkenyl, and C_{1-4} alkyl substituted with cycloalkyl, and R^3 is selected from halogen and CN.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/001449

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D473/04 C07D473/06 A61K31/522 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 389 282 A (BEECHAM - WUELFING GMBH & CO. KG; BEECHAM GROUP P.L.C; SMITHKLINE BEEC) 26 September 1990 (1990-09-26) cited in the application claims 3,13,15; examples 15-17,25	1-17
X	WO 92/09203 A (SMITHKLINE BEECHAM CORPORATION) 11 June 1992 (1992-06-11) claims 1,6,7,11	1-17
X	WO 99/20280 A (SMITHKLINE BEECHAM CORPORATION; GRISWOLD, DON, E; CHRISTENSEN, SIEGFRI) 29 April 1999 (1999-04-29) claims 1,6,7,12	1-17

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 2005	23/05/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/001449

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93/16699 A (SMITHKLINE BEECHAM CORPORATION) 2 September 1993 (1993-09-02) claims 1,6,7,12	1-17
X	ARCH, JONATHAN R. S. ET AL: "Inhibition of type 4 cyclic nucleotide phosphodiesterase by 8-chloroxanthines" ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) , 329(4), 205-208 CODEN: ARPMAS; ISSN: 0365-6233, 1996, XP008046719 compounds 2,19	1,2,5-7, 11
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X	SMELLIE, F. W. ET AL: "Alkylxanthines: inhibition of adenosine-elicited accumulation of cyclic AMP in brain slices and of brain phosphodiesterase activity" LIFE SCIENCES , 24(26), 2475-81 CODEN: LIFSAK; ISSN: 0024-3205, 1979, XP008046723 table 1	1-17
X	KATTUS, ALBERT A. ET AL: "Diuretic activity of compounds related to xanthines, uracils, and triazines as determined in dogs" BULLETIN OF THE JOHNS HOPKINS HOSPITAL , 89, 1-8 CODEN: JHHBAI; ISSN: 0097-1383, 1951, XP008046730 table 1	1-17
X	KATSUSHIMA T ET AL: "STRUCTURE-ACITIVITY RELATIONSHIPS OF 8-CYCLOALKYL-1,3-DIPROPYLXANTHINES AS ANTAGONISTS OF ADENOSINE RECEPTORS" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 33, 1 July 1990 (1990-07-01), pages 1906-1910, XP000611869 ISSN: 0022-2623 page 1909, right-hand column, line 28	11
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2005/001449

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 12,13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/001449

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Information on patent family members

International Application No
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